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CONTENTS

No. 1. *JANUARY* 1954

ε-Caprolactam.
M. W. GOLDBLATT, MURIEL E. FARQUHARSON, GEOFFREY BENNETT, and BERYL M. ASKEW 1

The Reaction of Rats to Diets Containing Octamethyl Pyrophosphoramide (Schradan) and 00-Diethyl-S-Ethylmercaptoethanol Thiophosphate (" Systox ").
J. M. BARNES and F. A. DENZ 11

Sickness Absence before the First Clinical Episode of Coronary Heart Disease.
J. A. HEADY, J. N. MORRIS, F. J. LLOYD, and P. A. B. RAFFLE 20

Pilot Trial of an Antihistaminic Drug in the Control of " Tetryl " Dermatitis.
W. A. BAIN and GRIZEL H. THOMSON 25

Perforation of the Nasal Septum due to Soda Ash. R. MCL. ARCHIBALD 31

The Effect of the Drinking Pattern on Water Economy in Hot, Humid Environments.
R. A. KENNEY 38

The Mill Reek and the Devonshire Colic. ANDREW MEIKLEJOHN 40

Miscellanea :

Beryllium Granuloma of the Skin. HENRY LEDERER and JOHN SAVAGE 45

First Conference of the British Occupational Hygiene Society 49

Occupational Hygiene in Great Britain. THOMAS BEDFORD 50

Measuring the Workers' Environment. S. A. ROACH 54

The Problem of Chemical Toxicity. D. G. HARVEY 58

Occupational Hygiene and the Industrial Designer. J. E. BRAHAM 61

Book Reviews 63

Abstracts 69

No. 2. *APRIL* 1954

Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Part I. The Role of Aniline, Benzidine, Alpha-Naphthylamine, and Beta-Naphthylamine.
R. A. M. CASE, MARJORIE E. HOSKER, DREVER B. MCDONALD, and JOAN T. PEARSON 75

Tumours of the Urinary Bladder in Dogs after Ingestion of 4-Aminodiphenyl.
A. L. WALPOLE, M. H. C. WILLIAMS, and D. C. ROBERTS 105

An Industrial Health Service in Norway. HAAKON NATVIG 110

Fatal Emphysema in Two Men Making a Copper Cadmium Alloy.
RONALD E. LANE and A. C. P. CAMPBELL 118

A Study of Boils at Three Collieries. O. P. EDMONDS, R. H. P. FERNANDEZ, and L. B. BATES 123

Individual Differences in Accident Susceptibility Among Coal Miners. J. W. WHITFIELD .. 126

The Toxicity of Nitrogen Pentoxide. W. M. DIGGLE and J. C. GAGE 140

The Development of Lymph Nodes after Injection of Flint of Variable Size into the Lungs of Rats. G. NAGELSCHMIDT, E. S. NELSON, E. J. KING, and C. V. HARRISON 145

The Effect of Oiling the Cotton on the Airborne Contamination in Card Rooms.
D. G. DRUMMOND, MARY HAMLIN, J. K. DONOGHUE, and F. BROWNSETT 151

Miscellanea :

A Simple Micromethod for the Determination of Lead in Small Amounts of Blood.
P. E. CORNISH and D. O. SHIELS 156

Three Approaches to the Study of Personality. ALASTAIR HERON 159

Book Reviews 161

Abstracts 165

No. 3. *JULY* 1954

Some Toxic Properties of Dimethylnitrosamine. J. M. BARNES and P. N. MAGEE 167

A Report on 235 Cases of Erysipeloid in Aberdeen. D. M. PROCTOR and I. M. RICHARDSON 175

Raynaud's Phenomenon in Workers with Vibratory Tools. R. P. JEPSON 180

The Treatment of Complicated Pneumoconiosis with Isoniazid.
W. E. MIALL, P. D. OLDHAM, and A. L. COCHRANE 186

Silica and Collagen in the Lungs of Silicotic Rats Treated with Cortisone.
B. D. STACY and E. J. KING 192

The Development of Compensation for Occupational Diseases of the Lungs in Great Britain.
ANDREW MEIKLEJOHN 198

Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Part II: Further Consideration of the Role of Aniline and the Manufacture of Auramine and Magenta (Fuchsine) as Possible Causative Agents. R. A. M. CASE and JOAN T. PEARSON .. 213

Thermal Conditions in Warships Refitting at H.M. Naval Base, Singapore.
G. SOUTHWELL-SANDER 217

Miscellanea :

Some Personal Observations on Industrial Health in the United States of America.
BRYAN HARVEY 222

Second Conference of the British Occupational Hygiene Society. R. J. SHERWOOD .. 227

Obituary :

Edward Provan Cathcart 229

Raymond Hussey 229

Book Reviews 230

Abstracts 232

No. 4. *OCTOBER* 1954

Carbon Disulphide Poisoning in Viscose Rayon Factories. ENRICO C. VIGLIANI 235

Infective Pneumoconiosis. 1. The Influence of Dead Tubercle Bacilli (B.C.G.) on the Dust Lesions Produced by Anthracite, Coal-mine Dust, and Kaolin in the Lungs of Rats and Guinea-pigs.
DAPHNE ATTYGALLE, C. V. HARRISON, E. J. KING, and G. P. MOHANTY 245

Coronary Heart Disease in Transport Workers. A Progress Report.
J. N. MORRIS and P. A. B. RAFFLE 260

Bursitis of the Shoulder in Coal Miners Using Boring Machines.
T. A. HUNT, O. P. EDMONDS, and R. H. P. FERNANDEZ 265

A Social and Occupational Study of the Causes, Cost, and Prevention of Infections of the Hand. RUTH WILKES 269

Soap Wrappers' "Jig." P. C. WASON 279

A Size-selecting Sampler for Airborne Dust. B. M. WRIGHT 284

A Follow-up Study of Pneumoconiosis in an Iron Foundry and Some Investigations into the Effect of Foundry Dust in the Lungs. G. F. KEATINGE and H. E. HARDING .. 289

An Investigation of Warts Prevalent among Workers in the Reduction Works of the Aluminium Industry. R. LOCKHART, M.C. 296

Miscellanea :

Some Recent Inquiries and Current Problems in the Social Organization of Industry.
D. H. ALLCORN 301

Occupational Mortality :

Cancer of the Respiratory Tract. RICHARD DOLL 305

Transport Workers. L. G. NORMAN 305

Book Reviews 307

Abstracts 312

Index 315

Brit. J. industr. Med., 1954, **11**, 1.

ε-CAPROLACTAM

BY

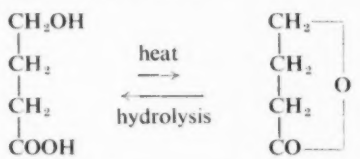
M. W. GOLDBLATT, MURIEL E. FARQUHARSON, GEOFFREY BENNETT, and BERYL M. ASKEW

From the Industrial Hygiene Research Laboratories, Imperial Chemical Industries, Ltd., The Frythe, Welwyn, Herts.

(RECEIVED FOR PUBLICATION JULY 23, 1953)

Lactams are internal amides of amino-acids as lactones are internal esters of hydroxy acids. Thus :

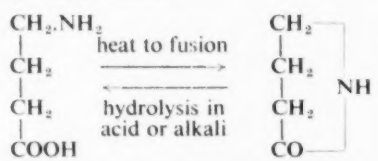
γ-Hydroxy butyric acid on losing one molecule of water gives γ-butyrolactone



The formation of lactones is an example of a general tendency of carbon chains to form five or more membered rings when the appropriate conditions are created. The lactone is readily hydrolysed to the hydroxy acid.

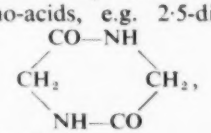
Similar types of change are brought about by heating γ, δ, ε, and ζ amino-acids to the temperature of fusion, thus :

γ-amino butyric acid loses one molecule of water and gives γ-butyrolactam



The δ-lactam of valeric acid is a six-membered ring and the ε-lactam of caproic acid is a seven-membered ring.

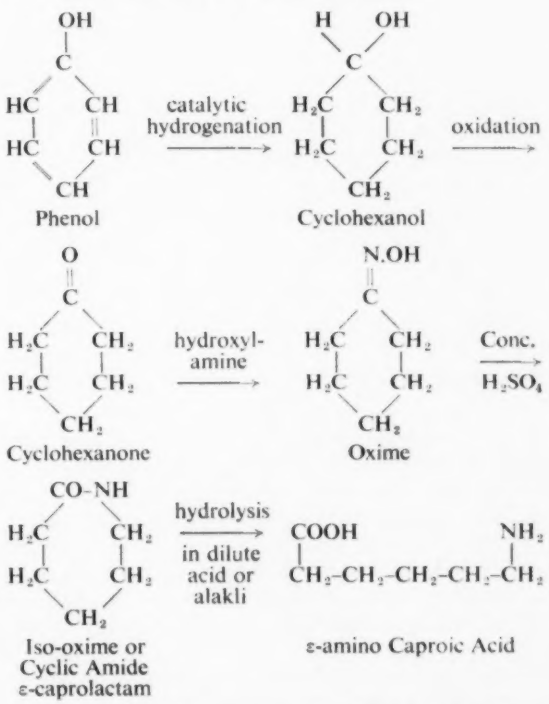
Cyclic amides are foreign to the animal body although they are readily formed by the condensation of amino-acids, e.g. 2·5-dioxo-piperazine

from glycine 

, by the action of dehydrating agents.

Manufacture of ε-Caprolactam and its Polymer

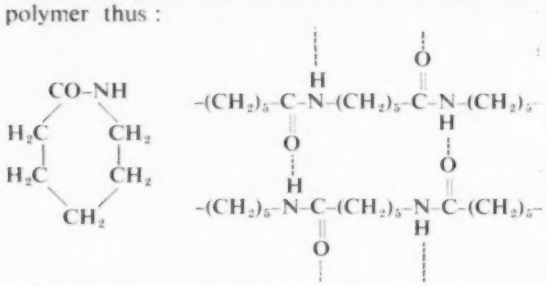
The general method for the preparation of δ, ε, and ζ lactams and their parent amino-acids is the formation of the appropriate cyclic ketones from which, by way of the oximes, the cyclic amide is produced by the action of concentrated sulphuric acid. The last stage is known as the Beckmann transformation. Thus, starting from phenols, the intermediate reactions are as follows :



This manner of preparation of the lactam from phenol recalls in its earlier stages the first reactions

in the synthesis of the linear super-polyamide nylon, in which the alkaline oxidation of cyclohexanol or cyclo-hexanone yields the di-basic adipic acid, which on being melted together with hexamethylene diamine gives the polyamide. Since two molecules each with six carbons are involved, the polymer is referred to as " nylon 66 ".

The " peptide " or amide link –CO–NH– will be familiar. In the nylon synthesis this link arises from two sources which give rise to the salt. Cross linking at the nitrogen atom also occurs. ε-Caprolactam can, by heating its aqueous solution to 260° C. at ordinary pressures, be transformed into a linear polymer thus :



This polymer, from which the synthetic fibres are spun, is a German discovery known as " perlon L ". It is unusually pure for a technical product, but is stated to contain normally approximately 1% of the monomer. Perlon L possesses a crystalline structure and in its physico-chemical properties is most readily compared with a metal. Its molecular weight is about 20,000 (Gabler, 1948).

Perlon U is the polymer derived from the condensation product of hexamethylene di-isocyanate and 1·4-butane diol.

Grilon is another polymer envisaged which will involve the condensation of ε-caprolactam by heat and pressure.

Working Conditions in the Manufacture of Perlon L

Experience of the manufacture of " perlon L " is greatest in Germany. Hohensee (1951) has given the most recent account of the working conditions in which the polymer is manufactured and the pharmacological properties of ε-caprolactam. The batch process is carried out in closed autoclaves which are opened only to charge fresh monomer. At the lower pole of these autoclaves there are the spinneret feeds : the extruded fibres emerge straight into the air, solidify, and are wound on bobbins.

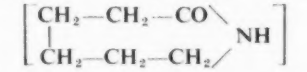
The atmosphere in the spinning rooms was found to contain 61 mg./m.^{3} and that of the laboratories 16–17·mg./m.^{3} as lactam (determination by passage of air into strong acid and estimation of ammonia nitrogen in the Kjeldahl manner). The vapour contamination consists of lactam at various stages of polymerization (dimer and trimer mainly), as well as lactam itself. The vapours condense in the cold air and dust deposits on door lintels, window frames, and beams both as a film and in crystalline form. At the high atmospheric concentrations given above it is not surprising to find that a bitter taste is experienced.

Hohensee (*loc. cit.*) reports that some workmen in the spinning section complained that at the end of the shift they were irritable, nervous, uncontrolled, and in some measure mentally confused. The symptoms were alleged to be aggravated when particularly dusty jobs (e.g. frequent changing of the spinnerets) were undertaken repeatedly during the day, with the occurrence of epistaxis, upper respiratory catarrh, with dry and splitting nose and lips. Other workers complained of flatulence, heartburn, and a heavy feeling in the stomach. All these symptoms disappeared after a period in the fresh air. The epistaxis and respiratory catarrh were attributed by Hohensee to the local irritant action of the lactam dust.

As these were the sole complaints and no other pathological disturbances were reported from the factory, in spite of obviously intense exposure to dust and vapour of monomer and polymers, it was concluded with some assurance that the toxic properties of the materials are not severe.

Properties of ε-Caprolactam

ε-Caprolactam or cyclohexanone iso-oxime



is a white crystalline solid and is extremely soluble in water. Recrystallized from ether it yields beautiful transparent rhombs with a melting point of 68° to 70° C. The compound tends to take up water in warm, humid air. ε-Caprolactam is readily hydrolysed to ε-amino caproic acid by heating in dilute mineral acid or alkali. It is stable in aqueous solution at 100° C.

ε-Amino caproic acid was prepared in our experiments from the lactam by hydrolysis in N.HCl, removal of the Cl by Ag_2O, precipitation of excess silver as sulphide and recrystallizing from the concentrated, aqueous solution by adding ethanol in which the amino-acid is practically insoluble. It crystallizes from cold alcohol in transparent, flat, hexagonal prisms. Its melting point is 201° to 202° C. It gives the ninhydrin reaction.

Toxicology of ε-Caprolactam

In the section on lactams Richter (1934–47) states that "the amino acids are not poisonous, but that the γ and δ lactams are violent, strychnine-like poisons, affecting the spinal cord and producing convulsions; ε-caprolactam . . . acts, physiologically, as a nerve poison". Lactams have weakly acid and weakly basic properties.

The first significant contribution to the toxicology of these compounds seems to have been that by Jacobj, Hayashi, and Szubinski (1903), although Jacobj had already shown in 1901 that the cyclic iso-oximes are powerful convulsants. Jacobj and others, interpreting their physiological results, stated that the effect of introduction of the +NH group into the ring of cyclic ketones was to replace a motor and central paralysis by a stimulant action of the "medullary convulsion centre" and later paralysis in the medulla.

They go on to say that the relatively simple cyclic iso-oximes (lactams) (piperidone, hexanone-iso-oxime, suberone-iso-oxime, and probably also pyrrolidone) produce convulsions in frogs and mice and must be included in the picrotoxin group. The convulsions are not reflex in type (i.e. strychnine-like); they are typically clonic in character and produced, they say, "durch Erregung des in der Medulla gelegenen Krampfzentrums". ε-Caprolactam, then, according to Jacobj and others is quantitatively the least toxic of these iso-oximes or lactams.

The description of the effects of ε-caprolactam in mice given by these authors may be summarized thus: the effects can be observed with a dose of 0·5 g./kg. subcutaneously; there is a mild increase in reflexes; intermittent muscle twitches appear and these develop into clonic convulsions; the convulsions are discontinuous and between onsets the animals are "narcotized" (a term used by the authors to indicate maintenance of uncomfortable postures); the animals emit cries; the clonic change over to tonic convulsions and animals die in the latter stage.

Hohensee's results for ε-caprolactam gave the L.D.50 values for mice as 0·75 g./kg. (subcutaneous), 0·58 g./kg. (intraperitoneal), 0·48 g./kg. (intravenous), and the L.D.100 was 1·20 g./kg. (by mouth).

These values are of the same order as those obtained by Jacobj and others (*loc. cit.*) and Dieke, Allen, and Richter (1947). Mice sustained without sequelae 42 daily doses of 50 mg./kg. and 150 mg./kg. by mouth and similar doses subcutaneously. Guinea-pigs sustained 26 to 30 daily exposures of five to eight hours to the vapour of a lactam melt (maximum temperature 180° C.) without any pathological effects. Application of 5% and 10% solution to the shaven skin of guinea-pigs, to the corneae of rabbits, and to the skin of human subjects gave no irritant reaction. In the rabbit 10 mg./kg. intravenously led to an ephemeral rise in blood pressure, and 50 mg./kg. in the cat was also pressor (20 mm. Hg), the effects passing off in 20 to 25 minutes. The pressor effect was not prevented by decapitation or vagotomy or atropine. Morphine inhibition of respiration in the rabbit was reversed by caprolactam, 500 mg./kg. being equivalent to 50 mg./kg. cardiazol.

The conclusions reached by Hohensee (*loc. cit.*) may be paraphrased thus: acute poisoning of human subjects by ε-caprolactam is impossible even in unfavourable industrial conditions; chronic absorption may proceed at high levels for extended periods without toxic effects: the low volatility of the compound and very high doses required renders poisoning by inhalation most improbable.

Toxicological Experiments

Nylon 66 is being developed in Great Britain and as the monomer (and lower polymers) is not only used in the manufacture but is present also in the final product, it was necessary to make sure that it was not likely to be a serious hazard in spite of its convulsant properties.

Hohensee's findings are a sufficient indication of the low quantitative toxicity. Our object was not to repeat his experiments, but, among other things, to observe what happens at different dose levels.

The ε-caprolactam used in our experiments had a melting point of 68° C. It is extremely soluble in water and ethanol, relatively poorly soluble in ether and the lower glycols, but soluble in chloroform and trichloroethylene to the extent of 1 g./ml.

Effects of Intraperitoneal Injection of ε-Caprolactam in Rats

Albino rats were used which belonged to our colony maintained for years in good health and reproductive capacity.

All injections were given in 0·5 ml. distilled water.

Toxic signs begin to appear clearly in many cases at 350 to 400 mg./kg., but recovery is general. At about 500 to 600 mg./kg. these signs are more marked and there are cries, tremors, apprehension, depression of temperature, and sometimes chromodacryorrhoea. But again there is recovery. In general, with our animals, we have not had deaths at doses below 800 mg./kg. Even 800 mg./kg. is not always

a fatal dose (mortality 66%) in spite of the appearance of delayed spasms.

At 900 mg./kg. death is certain, but may be delayed for a considerable time, and at 1,000 mg./kg. death is invariable in a few minutes. Convulsions are, when fully established, epileptiform, violent, and intermittent, and accompanied by salivation and bleeding from the nares. Judging from the condition of the corneal reflex and the fall in temperature and the tendency to lie quiescent between convulsions, there is also central depression.

Disturbances in heat regulation are a regular feature of the action of convulsant poisons. In the case of ε-caprolactam the marked fall in temperature when observed is best seen in the periods of depression between convulsive attacks. However, the fall in temperature may occur even in the absence of convulsions, but there is always an accompanying depression. Death was always due to respiratory paralysis, the heart ceasing to beat some minutes later.

If recovery occurred, there were no sequelae whatever the dose.

Intravenous Injection of ε-Caprolactam in Rabbits

Six rabbits were injected intravenously with doses ranging from 100 mg./kg. to 300 mg./kg. The effect was that of an intense, transient stimulation of the medulla, in many respects similar to that produced by picrotoxin at doses of 200 mg./kg. and over. There were no deaths.

The signs observed were apprehension, salivation, accelerated respiration, cries, muscular tremors, convulsions, opisthotonus, mydriasis. No fall in rectal temperature was noted. The rapidity of onset and transience in the case of intravenous injection is probably due to a rapid fall from the effective concentration by virtue of rapid removal from the blood or metabolism, or both.

There is thus no doubt that ε-caprolactam is a convulsant poison in both the rat and the rabbit.

On the other hand, the toxic properties are lost after the compound is hydrolysed to ε-amino caproic acid, even an intraperitoneal dose corresponding to that invariably fatal to rats (1 g./kg.) being totally without effect.

Although Thomas and Goerne (1914) recorded that ε-amino caproic acid is not "indifferent", 1·5 g./kg. subcutaneously in a rabbit producing death in 10 hours, no convulsive effects were recorded, and the necropsy of the animal used showed rather dubious changes.

It seems reasonable to conclude that hydrolysis *in vivo* would be an effective mode of detoxication.

Effect of Narcotics on the Convulsions Produced by ε-Caprolactam

It is common clinical practice to use intravenous barbiturates to combat convulsions, the danger being, however, that the barbiturate may produce so powerful a depression that it, in turn, becomes a cause of death. The short-acting barbiturates are the agents of choice. Conversely, convulsants, (e.g. picrotoxin, cardiazol) as symptomatic antidotes to narcotics are less effective and dangerously high doses may be required.

In testing the value of a chemical or a symptomatic antidote to a toxic agent, it is usual to administer the antidote after the toxic agent has begun to exert its effect. We used "veronal", the sodium salt of 5·5 di-ethyl barbituric acid (long acting), and tested (*a*) ε-caprolactam after "veronal", (*b*) ether after ε-caprolactam, and (*c*) "veronal" after ε-caprolactam.

Veronal Followed by Lactam.—Veronal is tolerated by rats in very high doses. Thus, we have found 120 mg./kg. intraperitoneally leads to incoordination and drowsiness; 240 mg./kg. produces narcosis; 360 mg./kg. deep narcosis and only 33% deaths. In all there is a considerable fall in temperature. In man the narcotic dose of "veronal" is about 0·3 to 0·5 g. by mouth, and the fatal dose lies between 4 g. and 10 g., i.e. between 60 mg./kg.and 150 mg./kg. approximately.

The inhibition of the action of the lactam by "veronal" is unequivocal as is also that of the "veronal" by the lactam.

Simultaneous intraperitoneal administration of 36 mg./kg. "veronal" and the invariably fatal dose of 1 g./kg. ε-caprolactam to three rats led to epileptiform convulsions, cries, chromodacryorrhoea, loss of corneal reflexes, and bitten tongue, but no deaths. If an interval is allowed to elapse between the barbiturate and the lactam injections, complete absence of all signs of ε-caprolactam effects can be obtained.

The dose of "veronal" is naturally a determining factor, for whereas 36 mg./kg. of "veronal" can inhibit the effects of 1 g./kg. of ε-caprolactam even after an interval of about two hours, 14 mg./kg. "veronal", effective even after 60 minutes, is ineffective after two hours.

The inhibition of the convulsive action of ε-caprolactam by the barbiturate is not more striking than the inhibition of the narcotic effect of the latter by the former. Thus, 1 g./kg. ε-caprolactam administered 21 minutes after the narcotic dose of "veronal" (240 mg./kg.) prevented all signs of narcosis, the animal surviving without sequelae.

Ether Narcosis after ε-Caprolactam.—If a lethal dose of ε-caprolactam be injected intraperitoneally in rats (1 g./kg.), the convulsions which rapidly follow can be controlled by ether inhalation and the animal maintained alive for many hours. If the ether control is stopped the emergence from the narcotic stage is accompanied by convulsions which can be extremely violent. These can be controlled again by ether and the process repeated for many hours. The conclusion seems inescapable that the lactam is maintained at convulsive levels either in the blood or in the central nervous system, and that detoxication is either inhibited or very slow in these conditions.

It would appear, therefore, that narcosis with a volatile anaesthetic like ether must be maintained for a considerable time if the danger from an ordinarily lethal dose of ε-caprolactam is to be overcome. Ether is less effective than "veronal" in combating the convulsive action of ε-caprolactam.

ε-Caprolactam Followed by Veronal.—Since the invariably fatal dose of lactam in rats of 1 g./kg. intraperitoneally produces death in a very few minutes, little time is available to take antidotal measures. A test dose of 0·8 g./kg. ε-caprolactam was therefore taken which, while producing severe symptoms, does not kill all animals. Two groups of six rats each were taken. One group received 0·8 g./kg. ε-caprolactam intraperitoneally, and the other group the same dose followed by an intraperitoneal injection of "veronal" (36 mg/.kg.) as soon as severe toxic signs appeared.

Severe signs appeared in both groups, but the mortalities were respectively 4/6 and 1/6.

A marked feature in the groups given "veronal" as well as ε-caprolactam was bleeding from the nares, even when convulsive movements were slight.

Long-term Administration of ε-Caprolactam to Rats

Although the gross acute toxicity of the compound is manifestly low, it was considered desirable to carry out a long-term experiment using the growth rate of rats as an index of insidious effects.

Two groups, each of six rats, were taken from two litters of the same age and, after a few days' maintenance in separate cages to accustom the animals to solitary life, one (Group E) had its water supply replaced by an aqueous solution of ε-caprolactam, 0·75 g. per 100 ml. The other (Group C) was the control group.

This concentration had been found in preliminary trials to be the highest the rats would accept.

The solid part of the diet was the same for both groups and was identical with that used for years in this laboratory, providing excellent growth and health. Fluid intake was measured daily. Weights of the animals were determined at frequent intervals. The experiment continued for 118 days. The average weights of both groups were identical at the onset of the experiment at 124 g. Table 1 summarizes the findings during the first 70 days of the experiment.

TABLE 1

—	Group C (6 rats)	Group E (6 rats)
Initial average weight	124 g.	124 g.
Average weight after 70 days	319 g.	287 g.
Total fluid intake per kg. body weight	10·33 litres	6·22 litres
Total lactam ingested per kg. body weight	0	46·65 g.
Average lactam ingested per kg. per day	0	0·667 g.

At this stage the lactam was withdrawn, with the result that in the succeeding 20 days Group E reached an average weight of 328 g. while Group C remained at 320 g.

In the succeeding 29 days Group C was put on the lactam solution, while Group E continued on tap water. At the end of this period the average weights were Group C 336 g., and Group E 356 g.

It thus appears that the depression in growth seen in Table 2, and attributable to the great diminution in fluid intake, is completely reversible. During the whole period of experiment neither group of animals showed any signs of ill-health. It is concluded, therefore, that growing rats will continue to ingest (and, we assume, absorb) 0·667 g./kg./day for long periods with no other sign of disturbance than a depression of the rate of growth.

Effect of ε-Caprolactam on Blood Pressure and Respiration

Blood Pressure.—According to Hohensee (*loc. cit.*) 10 mg./kg. ε-caprolactam produces an ephemeral rise in blood pressure in rabbits. In cats, 50 mg./kg. produces a rise in blood pressure of 20 mm. Hg, and the rise is said to have been maintained for 20 to 25 minutes. This rise occurred also in decapitated, vagotomized, and atropinized cats.

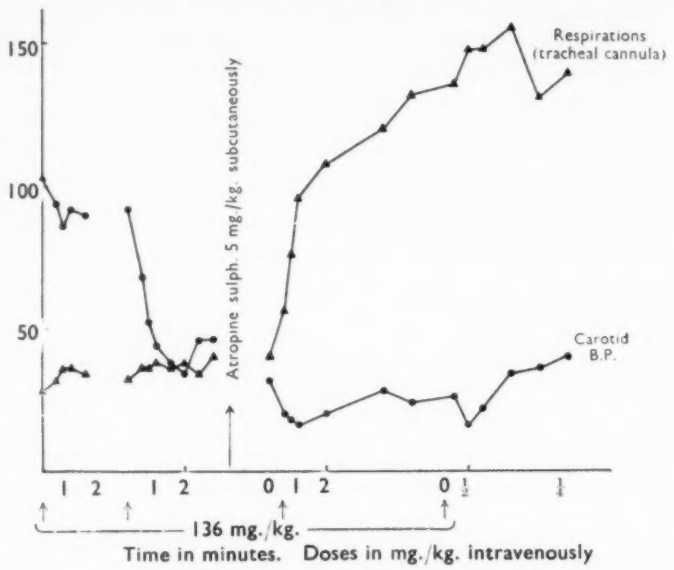
However, there is sometimes shortly after the injection an initial fall in blood pressure. On the isolated frog's heart, there is a passing inhibition at $\frac{1}{10^4}$ to $\frac{1}{5 \times 10^3}$ but later there is a positive inotropic effect. Hence Hohensee suggests that there may be enough cardiac inhibition in the mammal to

produce the passing depressor effect and thereafter the rise will occur as a result of the stimulus to the force of the heart.

Our experiments were designed simply to see if any significant change in blood pressure could be produced by intravenous injection.

Fig. 1 shows the effect of moderate to large single doses of ε-caprolactam in the rabbit. Five repeated doses of 23 mg./kg. were required to produce a steady rise in blood pressure from 82 to 100 mm. Hg, a fifth dose no longer producing any effect, but in the following 20 minutes the pressure fell to 50 mm. At this point an injection of 230 mg./kg. led to a sharp but temporary fall to 34 mm., with an accompanying rise in respiratory rate. The conditions *quo ante* were re-established some four minutes after this injection.

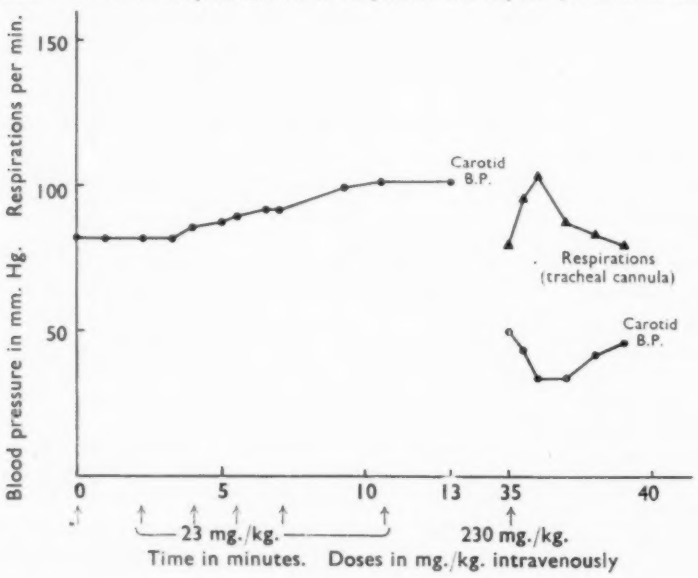
FIG. 2.—Effect of ε-caprolactam on blood pressure and respiratory rate of cat.



The cat (Fig. 2) responded invariably to 136 mg./kg. with a fall in blood pressure and a significant rise in respirations. Two doses brought the blood pressure down from an initial 102 mm. to 46 mm., and the respirations up from 28 per minute to 40 per minute. Atropinization (5 mg./kg. subcutaneously) did not affect respiration, but the subsequent injection of 136 mg./kg. ε-caprolactam increased the respiratory rate over threefold. Convulsions appeared and were most violent, lifting the animal from the table. The convulsions appeared after the great rise in respiratory rate, and did not increase the rate to any marked extent. Vagotomy does not prevent the depressor or the respiratory stimulant effect.

In the next experiment it will be seen that respiration is accelerated in the total absence of convulsions.

FIG. 1.—Effect of ε-caprolactam on blood pressure and respiratory rate of rabbit.



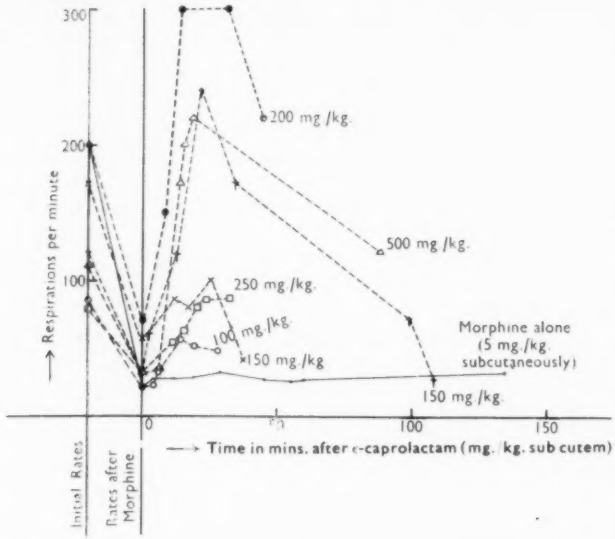
Respiration.—Although we have seen the intense respiratory stimulation induced by ε-caprolactam in the anaesthetized, atropinized cat, it was felt desirable to repeat the test in the unanaesthetized animal in which the respiratory centre had been markedly depressed.

Fig. 3 shows the effect of various subcutaneous doses of ε-caprolactam on the slowed respiratory rate of rabbits injected subcutaneously with 5 mg./kg. morphine hydrochloride.

The doses of lactam varied from 100 mg./kg. to 500 mg./kg. and the response was clear in all cases.

The sensitivity of the respiratory centres varied, the quantitative response not corresponding to the size of dose.

FIG. 3.—Effect of subcutaneous ε-caprolactam on respiratory rate of morphinized rabbits.



The maximum stimulation of the centre occurred at about 20 minutes (14–31) after the lactam injection, at which time probably the highest blood lactam concentration had been reached.

Slight to severe tremors were produced by all the doses of lactam but no convulsions.

Inhalation of ε-Caprolactam Dust

Hohensee (*loc. cit.*) points out that the low volatility of this compound renders poisoning by this route most improbable, and substantially impossible. He exposed guinea-pigs to air which had been passed over a lactam melt at 180° C. (concentration in atmosphere 51 mg./m.^{3}). Exposure for five to eight hours per day for 26 to 30 days resulted in no pathological effects nor any evidence of increased or abnormal mobility. Slight evidence of irritation of the nasal mucosa was noted.

In our experiments, three guinea-pigs were exposed to concentrations of very fine particulate dust produced by Gage's method (to be published), whereby very fine sprays of solutions can be delivered into a chamber so that the solvent evaporates and the fine dust concentrations are set up dynamically. The vast majority of the particles formed from the aqueous spray were below 5μ in size. The concentrations of ε-caprolactam (determined analytically) were varied on different days from 118 mg./m.^{3} to 261 mg./m.^{3}. The animals were exposed for seven hours daily for seven days. Except for occasional coughing, no adverse effects were noted.

The total amounts of the compound absorbed in our experiment and in that of Hohensee were clearly of the same order, and we draw the same conclusions.

Application of ε-Caprolactam to the Skin of Normal Human Subjects

It will be recalled that Hohensee (*loc. cit.*) applied 5% and 10% solutions of ε-caprolactam to the skin of guinea-pigs and of human subjects, as well as to the corneae of rabbits without finding evidence of irritant properties. Application of the 5% solution to the skin of one man and two women for 35 days of eight hours each led to no evidence of irritation. One of the women, who was pregnant (six months), showed a mild erythema after 20 days' application, and by the thirtieth day the experiment had to be stopped. The other two subjects showed no adverse effects whatever. The cause of the erythema in the pregnant woman was not clarified, but Hohensee evidently did not attach much importance to it.

In our experiments we applied 5% aqueous ε-caprolactam to the skin of the inner forearms of six normal persons (one fair girl, one dark girl, two fair men, two dark men) as a 4 cm. × 3 cm. patch test left in contact for 48 hours. There were no reactions produced by the ε-caprolactam.

In a second series of tests a 5% alcoholic solution of ε-caprolactam was applied by placing six drops on the same area : the alcohol was allowed to evaporate and the residue kept undisturbed in contact with the skin throughout the day. The process was repeated twice daily for four days. No irritant effects of any kind were produced.

Similar experiments were carried out with a 5% olive oil solution of ε-caprolactam, and again it was found with five subjects that no irritant effects were produced during four days of application twice a day.

Excretion and Metabolism of ε-Caprolactam

With so soluble a compound and so low a quantitative toxicity it was to be expected that excretion or detoxication (or both) would be rapid.

A simple process of detoxication would be to hydrolyze it, thus opening the ring and yielding the ε-amino acid. The ultimate disposal of this amino-acid would depend upon whether the organism could metabolize it.

In respect of the possible metabolism of this amino-acid, reference may be made first to the work

of Thomas and Goerne (1914) who, studying the origin of creatine, fed 13 g. of ε-amino caproic acid to five rabbits and recovered only 2·26 g. (17·4%) in the urine unchanged, and concluded that " the greater part of the acid must have been oxidized away ".

There are difficulties in formulating the breakdown in the body of the amino derivative of caproic acid. Dakin (1922) was unable to demonstrate the formation of acetone bodies or of glucose on administering lysine (α-ε diamino-caproic acid) to phloridzinized animals. More recently, Corley (1929) states that ε-amino caproic acid is not a sugar former in the completely phloridzinized dog.

In the following experiments the object was to establish the order of excretion of ε-caprolactam as such and as amino-acid. Rats and rabbits were used and the lactam was administered by intraperitoneal injection in aqueous solution. This mode of administration made less likely the interference of intestinal enzymes. To see if any lactam was excreted by the gut, the faeces were analysed for lactam.

The urine was collected in such a way that there was minimal contamination by faeces or food, and maintained frozen solid. Each day's collection was thawed out and made up to volume, filtered, and analysed for amino-N and lactam. Faeces were collected and analysed as below.

Determination of Amino-Acid in Urine

There are a number of difficulties which arise if amino-acid N is to be determined in urine in the presence of lactam which is readily hydrolyzed if the essential step of removing ammonia is performed at too high an alkalinity. After many experiments the following method was found satisfactory for determining amino-acid in the presence of lactam, the latter remaining intact.

Determination of Amino-acid N in Urine.—The day's urine is made up to a suitable volume (50 ml. in case of rat). A sample (20 ml.) was placed in a distilling flask set up for steam distillation, treated with $BaCl_2$ and made just alkaline to phenol phthalein with $Ba(OH)_2$. Ethanol (100 ml.) was now added (protein thus precipitated) and the ammonia was driven off with the alcohol by steam distillation. The considerably reduced volume was reduced to convenient proportions by azeotropic distillation with benzene (75 ml.) and ethanol (75 ml.) at reduced pressure. The final volume was made up to 50 ml., filtered, and 10 ml. was used for the determination by the formol method, the end-point being set by a water control.

The method is tedious, but yields very satisfactory results in the special circumstances for which it was devised.

Normal Excretion of Amino-acid N by the Rat.—The normal excretion of amino-N by rats in our colony fed on our standard cube diet was determined (Table 2).

Thus, in our rats, 31 out of 41 determinations fell within a range of 7 to 10 mg ; six exceeded 10 mg., and three were below 7 mg.

Determination of Lactam in Urine

For certain of our experiments the determination of ε-caprolactam in urine and faeces was necessary, and the following methods were used. ε-Caprolactam is satisfactorily soluble in chloroform, and we have found that this solvent can be used to determine the lactam in urine.

A 5 ml. sample of urine dilution (daily urine of laboratory animal made up to 50 ml.) is added drop-wise to a 15 g. anhydrous sodium sulphate or silica gel in a dry glass mortar. The contents are ground up without previous drying (drying at 100° C. will reduce yield very greatly) with 40 ml. $CHCl_3$ for 10 minutes.

The extract is decanted into a distilling flask. A second similar extraction and decantation is sufficient to remove from urine amounts of lactam less than 1 mg. per ml.

The $CHCl_3$ is now distilled in a boiling water bath and the residue hydrolysed with 5 ml. 2N HCl at the same temperature. The resulting amino-acid is determined by the formol titration.

The time required for complete hydrolysis is one and a half to two hours for a 0·1% solution. Extraction

TABLE 2
NORMAL EXCRETION OF AMINO-N BY RATS

Rat No.	Normal Daily Amino-N Excretion (mg. per 100 ml. urine)									Mean Value	Standard Error of Mean
1	4·3	12·3	8·5	7·7	7·7	—	—	—	—	8·1	1·43
2	8·6	10·2	8·9	10·2	7·7	6·6	7·5	7·1	10·0	8·6	0·46
3	9·6	10·0	9·6	8·3	8·1	7·2	10·0	7·1	12·5	9·1	0·56
4	8·6	10·2	8·9	10·2	7·7	6·6	7·5	7·1	10·0	7·7	0·55
5	9·6	10·0	9·6	8·3	8·1	7·2	10·0	7·1	12·5	8·2	0·66
						Grand mean				8·4	0·35

by this method from 0·1% aqueous solution was 73%, and from 0·1% in normal urine was 71%.

Determination of Lactam in Faeces

In experiments on the excretion of lactam it was necessary to determine possible excretion in the faeces.

The following was the method used :

The day's faeces were weighed, and 5 g. (or total faeces if less than 5 g.) was ground up with 15 g. anhydrous Na_2SO_4. The mass was extracted twice with chloroform at room temperature. The combined deep-green extracts were freed from chloroform by distillation in a boiling water bath. Some 20 ml. of distilled water was now added to the green extract and the flask replaced in the boiling water bath to remove traces of chloroform. When the volume has thus been reduced by about half, it is found that the highly pigmented matter remains adherent to the sides of the flask and the water extract is clear. The aqueous extract is now filtered into a flask, several washings combined and then hydrolyzed (2N HCl) at 100° C. for one and a half to two hours, and the resulting amino-acid determined titrimetrically.

Applying this method to rat faeces containing 50 mg. per 5 g. faeces, a yield of just over 72% is readily obtained. Appropriate correction was therefore made in individual determinations.

Excretion of Lactam and Amino-acid after Intraperitoneal Injection of Lactam

In the following experiments the excretion of lactam and amino-acid was determined after intraperitoneal injection of lactam in the quantities stated. The determination in urine continued in each case until no lactam could be detected in the urine.

No certain conclusion can be drawn from our figures (in Table 3). Tentatively we may say that circumstances may exist in the rat when the metabolism of ε-amino caproic acid appears difficult, and in such circumstances injected lactam can be largely accounted for by excreted lactam and amino-acid. The problem will be pursued in further experiments by the administration of ε-amino caproic acid, but we may refer again to Dakin (*loc. cit.*), whose results indicated that the metabolism of the natural di-amino caproic acid is not straightforward, and to Corley (*loc. cit.*).

Excretion of Lactam and Amino-acids by Rabbits after Intraperitoneal Injection of ε-Caprolactam

In similar experiments with three rabbits, 400 mg./kg. ε-caprolactam were injected intraperitoneally and analyses of urine and faeces continued for four days. The percentages of the dose appearing in the urine and faeces as lactam were 8·7, 22·3, 10·1,

TABLE 3

EXCRETION OF LACTAM AND AMINO-ACIDS BY RATS AFTER INTRAPERITONEAL INJECTION OF ε-CAPROLACTAM

Lactam Injected (mg. N.)	Lactam in Urine (mg. N)	Amino-acid* Excess in Urine (mg. N)	% of Dose Accounted for in Urine in Periods of 2 to 5 Days		
			As Lactam	As Amino-acid	Total
12·3	8	None detected	65	?	—
12·3	4	Not determined	32·5	?	—
12·3	4·5	Not determined	36·5	?	—
14·8	6·9	5·2	46·6	35·3	82
14·8	6·9	8·3	46·6	53·4	103
16·0	3·5	7·9	21·9	49·1	71
17·3	2·9	10·4	16·8	60·2	77
(Control values for amino-acid excretion determined during 9 days before injection)					
14·8	1·4	Dubious	10	?	—
14·8	3·4	8·9	22·8	60	83

Control values for amino-acid excretion determined during two to three days before injection.

and no additional amino-acid N could be detected in the urine.

It would thus appear that the rabbit can metabolize ε-caprolactam almost completely. Of the 2·24 g. lactam injected into these animals, 86% was not accountable for either as lactam or amino-acid. This finding agrees with that of Thomas and Goerne (*loc. cit.*).

We have not had an opportunity to study the utilization of ε-caprolactam in human subjects : this will perhaps be possible later when it is manufactured.

Discussion

The practical question is whether, in view of the experimental evidence, the assurance can be given that the hazard to operatives who might be exposed to considerable concentrations of the monomer (ε-caprolactam) is negligible. Hohensee (*loc. cit.*) gives this assurance on the grounds that the proportional acute fatal dose in man would be about 70 g., that chronic administration of high doses in animals is well tolerated, and that the low volatility of the compound renders toxic effects most improbable by inhalation. There is also the additional evidence that men have worked in high concentrations with only minor complaints, and that there is no evidence of direct skin irritation in human subjects. (Hypersensitivity may be found in some cases.) From a variety of pharmacological observations made by Hohensee (inhibition of the isolated gut,

inhibition of the frog's heart), and from our own demonstration of depressive action and ultimately respiratory paralysis, we must conclude that ε-caprolactam is a protoplasmic poison as well as a convulsant.

These effects are produced only by relatively large doses. It is the business of those responsible for industrial health to preclude the absorption of any such material, even if there is little chance of cumulation. Cumulation, indeed, is ruled out by the long-continued ingestion of the compound by our rats (0·67 g./kg./day).

The symptoms complained of by men exposed to high concentrations of monomer dust were irritability, nervousness, loss of control, and some confusion (Hohensee, *loc. cit.*). Such a consistent group of symptoms cannot be ignored. It is in close correspondence with what would be expected from the reaction of animals to sub-lethal doses.

It is too facile to suggest, as Hohensee appears to do, that most of these complaints were psychological or due to the odour and taste of the compound. The fact that the German workers only complained of those symptoms when exposed to a high concentration is in itself significant.

We take the view, therefore, that in spite of the quantitatively relatively low toxicity of ε-caprolactam, the possible effects of the exposure of workers to high atmospheric concentrations of the vapour or dust constitute a potential hazard. This view is taken because doses far below lethal in animals can continue to cause mild tremors, increased reflex activity, and apprehensiveness for many hours.

Summary and Conclusions

ε-Caprolactam is a convulsant poison in rats, rabbits, and cats.

Quantitative toxicity is very low by all routes. Pharmacological effects are, however, evoked in the intact animal by doses of about 100 mg./kg. and over.

It can be tolerated orally in the drinking fluid in large doses without toxic symptoms by growing rats for long periods. Because of its unpleasant taste, the growing animals voluntarily ingest only sufficient of the solution to assure growth, but at a level much below normal. This effect is completely and swiftly reversible.

ε-Caprolactam can prevent the narcosis induced by "veronal", and "veronal" can inhibit or stop the convulsions due to caprolactam.

In large doses it is a powerful respiratory stimulant and mild circulatory depressant. In smaller doses a slight pressor effect on the circulation can be produced.

ε-Caprolactam is not a skin irritant and no indication has been found that it could act as a sensitizing and dermatitic agent.

High concentrations of fine caprolactam dust (118 to 261 mg./m.^{3}) can be respired by animals for long periods without manifest adverse effects.

ε-Caprolactam is excreted by rats partly as lactam and partly as ε-amino-acid, and sometimes appears to be almost wholly accounted for in this way. It appears, therefore, that the ε-amino-acid may not be easily metabolized by the rat.

The rabbit, on the other hand, appears able to metabolize ε-caprolactam completely, a small proportion of unmetabolized lactam appearing in the urine after intraperitoneal injection of large doses. It is desirable to discover how the lactam is metabolized in man.

Whilst the likelihood of serious dangers to health from ε-caprolactam in the processes of manufacture and use is small, it is considered desirable to preclude the possibility of high concentrations in the working environment and to keep medical records of exposed men, especially concerning the circulatory, respiratory, and nervous systems.

We wish to thank Miss Anne Harrell for technical assistance.

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THE REACTION OF RATS TO DIETS CONTAINING OCTAMETHYL PYROPHOSPHORAMIDE (SCHRADAN) AND OO-DIETHYL-S-ETHYLMERCAPTOETHANOL THIOPHOSPHATE ("SYSTOX")

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The compounds octamethyl pyrophosphoramide (schradan) and OO diethyl S. ethylmercapto-ethanol-thiophosphate (" systox "*) are the active ingredients of certain insecticide preparations. Because they are actually taken up by the plants to which they are applied they have been termed " systemic " insecticides. The presence of these insecticides is responsible for the death of the insects feeding on the plants, and also poses a problem in assessing any toxic hazard that may arise from the consumption of the same plants or parts of them at a later stage by man.

Previous work with OO - diethyl O-p-nitrophenyl thiophosphate (E605, parathion) by Barnes and Denz (1951) has shown that rats which had received a diet containing 20 p.p.m. parathion for one year were apparently normal by the conventional standards of toxicity tests such as behaviour, rate of growth, mortality, and pathological changes in the tissues. Parathion inhibits the cholinesterase of animals to which it is administered, and Frawley, Hagen, and Fitzhugh (1952) observed a significant reduction of the cholinesterase activity of the blood and brain of rats receiving as little as 5 p.p.m. parathion in their food. The inhibition of cholinesterase is thus a more sensitive indicator of the absorption of parathion than the conventional tests for chronic toxicity.

In this paper both the general reaction and the specific effect upon cholinesterase in rats that had received several concentrations of schradan and " systox " in their diet are recorded. A number of differences in the reaction of the rats to the two compounds was observed and the findings also indicate the problem of assessing " chronic toxicity".

The formula of schradan is given in Fig. 1.

* Prepared by Messrs. Bayer of Leverkusen.

Pure schradan has very little activity as an inhibitor of cholinesterase *in vitro*. The material used in these experiments was a commercial preparation containing 65% of active ingredient. It also had a considerable activity and tested against rat brain and rat plasma cholinesterase *in vitro* it produced 50% inhibition at $8{\cdot}5 \times 10^{-5}$ M.

DuBois, Doull, and Coon (1950) stated that the acute oral lethal dose of schradan was 9–10 mg. per kg. for male and female rats.

The toxicity of the material used in these experiments was tested by oral administration of aqueous solutions. The average single lethal dose was 6·5 mg. per kg. for male and 27·5 mg. per kg. for female rats. The dose is expressed in terms of the active ingredient.

DuBois and others (1950) found that the daily injection of 1 mg. per kg. killed all rats within eight days but rats could tolerate a daily dose of 0·5 mg. per kg. for at least four weeks.

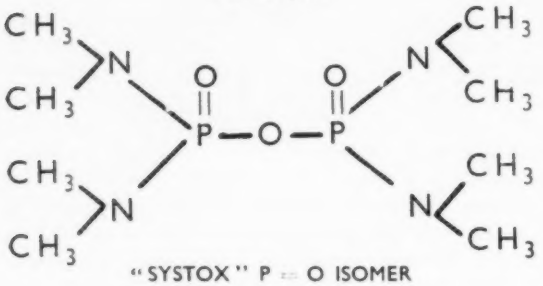
Rider, Ellinwood, and Coon (1952) in a small series of rats found that a daily dose of 0·5 mg. per kg. by injection raised the tolerance of rats so that they could then withstand a daily dose of 1·0 mg. per kg. which would otherwise have killed them.

" Systox " is known to be a mixture of isomers the formulae of which are given in Fig. 1 (Wirth, 1953 ; Gardiner and Heath, 1953). The material used in these experiments was analysed before the experiments were started and again some weeks after they had been concluded. On both occasions the sample was found to contain 48% of the P = O isomer. Wirth (1953) found that the L.D.50 for male rats given a single oral dose was 7·5 mg. per kg. for the P = S isomer and 1·5 mg. per kg. for the P = O isomer.

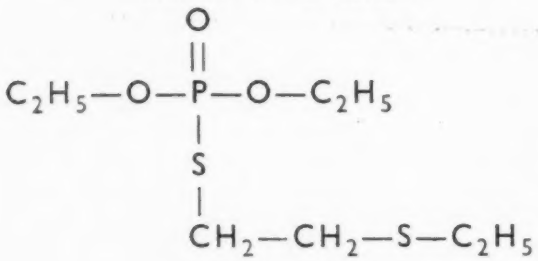
The material used in these experiments had an

approximate L.D.50 of 10 mg. per kg. for male rats and 4 mg. per kg. for female rats given orally as an alcoholic solution diluted 1 in 100 in water just before administration. The rats used in these experiments must have been less sensitive than those used by Wirth, for from his figures the L.D.50 for male rats should have been not greater than 3 mg. per kg. on the basis of the P = O isomer content alone.

SCHRADAN



"SYSTOX" P = O ISOMER



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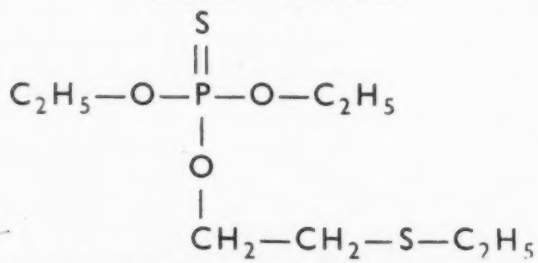


FIG. 1.—Formulae of schradan (octamethyl pyrophosphoramide) and the isomers of "systox" (0 0-diethyl ethyl mercaptoethanol thiophosphate).

The material used was tested against rat brain and rat plasma cholinesterase and produced a 50% inhibition in concentrations of 4×10^{-6} M and $2{\cdot}4 \times 10^{-6}$ M respectively.

Materials and Methods

Male and female albino rats from the same stock were used. They were individually marked but housed six to eight in a cage.

A stock diet (M.R.C. Diet 41) was available in a powder form but was fed to the rats as a stiff paste made by adding 70 ml. of water to each 100 g. A weighed quantity was given daily to each cage. In the later experiments the food remaining next day was weighed so that the daily intake could be estimated.

The drugs were administered by adding them to water used to prepare the paste from the dry diets. Stock solutions were made up so that a fixed volume (1 ml.) had to be added to each 100 g. of diet in order to provide the required concentration. Schradan was available as a commercial preparation containing 65% active ingredient. Since it was stable, stock solutions were made up in water. "Systox" was available as the active ingredients of commercial preparations. Stock solutions were made in ethanol.

Animal weights were recorded once or twice a week.

All animals were killed by carbon monoxide. Tissues for histology were fixed in Helly's fluid and after processing were stained with haematoxylin and eosin.

Cholinesterase determinations were by the methods of Nachmansohn and Rothenberg (1945) with details given by Aldridge (1950). Acetylcholine was used as the substrate so that the activity measured was that due to both the true and pseudo cholinesterase. The predominant enzyme in the rat brain is true cholinesterase and the organ was removed whole, weighed, and homogenized in an all-glass homogenizer.

In the first experiments the activity of whole blood was determined. This measured the combined activity of the true cholinesterase, which is present in the red cells only, and the pseudo-cholinesterase of the plasma. In later experiments these were determined separately. The personal error of the two technicians carrying out the determinations was also measured, and found to represent differences of 3 to 4% in the readings.

Results

Some details of the experiments that were carried out are given in Table 1. The experiments are numbered and reference to this number is made in subsequent tables.

Schradan.—The male rats on 50 p.p.m. were the only ones to show signs of poisoning. These were not severe and consisted of slight general weakness and persistent, fine, muscular fasciculations. These signs disappeared within 12 weeks and were not seen again during the 52 weeks of the experiment.

TABLE 1

FEEDING EXPERIMENTS CARRIED OUT WITH SCHRADAN AND "SYSTOX"

Compound	Experiment No.	Duration (weeks)	Concentration of Dose* (p.p.m.)	Numbers of Rats	
				Male	Female
Schradan ..	1	52	50	8	8
	—	—	10	8	8
	—	—	0	8	8
	2	13	10	12	—
	—	—	3	12	—
	—	—	1	12	—
	—	—	0	12	—
	3	4	1	12	—
	—	—	0·3	12	—
	—	—	0·1	12	—
	—	—	0	12	—
"Systox"	4	16	50	—	12
	—	—	20	—	12
	—	—	10	—	12
	—	—	0	—	12
	5	11	10	—	18
	—	—	3	—	18
	—	—	1	—	18
	—	—	0	—	18

*Dose is the amount of active ingredient added to the dry diet.

The rates of growth of the groups are given in Figs. 2 and 3. Only the male rats (Fig. 2) on 50 p.p.m. did not grow normally and they remained under weight for at least the first 18 weeks of the experiment (Table 2).

The significance of any difference between the weight of this group and the control animals was reduced in the later part of the experiment by the unusually wide scatter of weights in the control group.

During the year there were two deaths from unknown causes among the controls, and three rats from the 10 p.p.m. groups were killed because of middle-ear disease. There were no deaths among

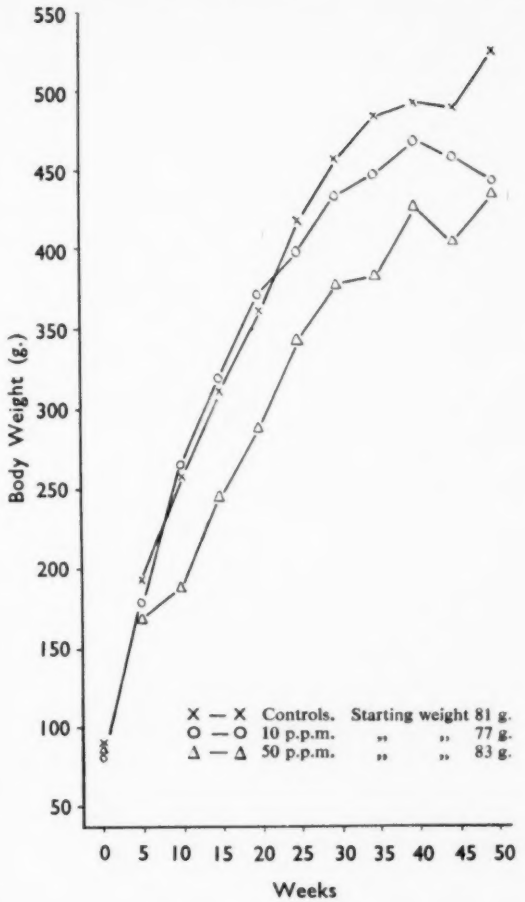


FIG. 2.—Weights of male rats on diets containing schradan (Experiment 1).

TABLE 2

COMPARISON BETWEEN MEAN WEIGHTS AND DAILY FOOD INTAKE OF MALE RATS ON 50 P.P.M. SCHRADAN AND CONTROLS

Time (weeks)	Food Intake*		Mean Body Weight (g.) with Standard Error		t	p
	Control	50 p.p.m.	Control	50 p.p.m.		
0	—	—	81	83	—	—
2	—	—	126 ± 10	114 ± 15	1·74	>0·1
7	—	—	250 ± 25	166 ± 12·5	8·04	<0·01
12	—	—	296 ± 37	221 ± 22	3·75	<0·01
17	7·15 ± ·26	6·9 ± ·06	358 ± 52	288 ± 29	3·1	<0·01
26	—	—	431 ± 86	350 ± 30	0·56	>·1
50	4·68 ± ·09	5·6 ± ·02	490 ± 100	456 ± 36	0·74	>·1

*Food intake is given as g. per rat per 100 g. body weight per day and is the mean of three successive weeks (Experiment 1).

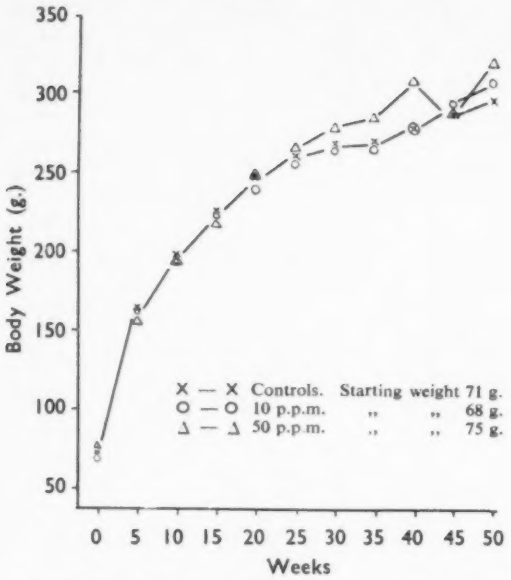


FIG. 3.—Weight of female rats on diets containing schradan (Experiment 1).

those on 50 p.p.m. but two were removed during the experiment for another purpose.

The food intake was not recorded until the sixteenth week of this experiment. The figures obtained during the sixteenth to eighteenth weeks show that the underweight males on 50 p.p.m. were eating a quantity per 100 g. body weight similar to that eaten by the controls (Table 2). The daily dose of schradan consumed by these rats was equivalent to 3·45 mg. per kg. per day or about half the single lethal dose.

The liver, kidney, and spleen of the rats were examined histologically. Special attention was paid to the liver because it has been shown that it is in the liver of the rat that schradan is converted to an active inhibitor of cholinesterase (Cheng, 1951). No pathological changes attributable to the action of schradan could be detected.

The results of determinations of the blood and brain cholinesterase activities are given in Tables 3 and 4.

At neither 10 p.p.m. nor 50 p.p.m. was there a marked reduction in the activity of the brain cholinesterase, but at both levels of feeding that of the blood cholinesterase was reduced. In this experiment (Table 3) it will be seen that the activity of the blood cholinesterase in the normal females was greater than that of the normal males. This has been described by others (Levine and Suran, 1951). However, at equal levels of schradan in the diet an almost equal reduction in activity of the blood cholinesterase of the two sexes was produced. At the time these rats were killed and the determinations made the females were eating 6·5 $\pm$ 0·38 g. food per 100 g. body weight per day which was 20% more than the males (5·4 $\pm$ 0·36).

Further experiments were done on male rats only in order to find out the lowest dose level of schradan that would produce a detectable depression of the blood cholinesterase activity, and for this, separate determinations of red cell and plasma cholinesterase were made in addition to those on whole blood. The figures for rats on diets containing 10, 3, 1, 0·3 and 0·1 p.p.m. schradan are given in Table 4. Although some of these experiments only ran for four weeks this gave time for the cholinesterase inhibition to reach a steady level as shown by the similarity of the figures obtained in the two experiments where 1 p.p.m. was fed. The experiments were done with an interval of several months;

TABLE 3

CHOLINESTERASE ACTIVITY OF BRAIN AND WHOLE BLOOD OF RATS RECEIVING 10 AND 50 P.P.M. SCHRADAN FOR ONE YEAR

Experiment 1	Drug in Diet (p.p.m.)	Male				Female			
		*ChE Activity	S.E.	No. of Rats	†% Activity	ChE Activity	S.E.	No. of Rats	% Activity
Brain ..	0	180·6	9·27	8	100	166·3	4·75	6	100
	10	142·6	21·69	3	79	154·7	10·09	7	92·6
	50	152·8	8·18	8	84	130·6	6·07	6	78·5
Blood ..	0	20·03	1·06	8	100	44·2	4·55	3	100
	10	10·59	1·29	3	52	25·59	2·48	7	57·9
	50	4·82	0·75	8	23·5	15·17	2·04	6	34·3

Acetylcholine was used as substrate by techniques of Nachmansohn and Rothenberg (1945) and Aldridge (1950).
*ChE activity = Mean μl. CO_2 evolved per minute per g. brain or ml. of blood.
† % activity = Activity expressed as percentage of control group.

TABLE 4

CHOLINESTERASE ACTIVITY OF BRAIN, WHOLE BLOOD, PLASMA, AND RED CELLS OF MALE RATS FED SCHRADAN

Experiment 2*	Drug in Diet (p.p.m.)	†ChE Activity	S.E.	No. of Rats	% **Activity	Experiment 3*	Drug in Diet (p.p.m.)	ChE Activity	S.E.	No. of Rats	% Activity
Brain	0	199·03	5·53	6	100	Brain.. ..	0	194·33	4·33	12	100
	10	162·26	6·75	6	81·5		1	191·56	2·53	12	98·5
	3	184·84	6·81	6	93		0·3	205·43	5·58	12	105·7
	1	188·9	5·45	6	95		0·1	198·34	5·21	12	102
Whole blood ..	0	18·58	1·17	6	100	Whole blood	0	15·39	0·39	12	100
	10	6·80	0·37	5	42·7		1	12·45	0·18	12	80·9
	3	10·29	1·06	6	57		0·3	15·79	0·21	12	102·5
	1	14·59	0·77	6	79·5		0·1	15·25	0·35	12	99·04
Plasma ..	0	11·27	0·94	6	100	Plasma ..	0	10·02	0·54	12	100
	10	5·65	0·22	5	49·7		1	9·48	0·47	12	94·6
	3	8·57	1·25	6	76		0·3	10·52	0·51	12	105
	1	10·87	0·71	6	96·4		0·1	10·22	6·54	12	102
Red cells ..	0	7·98	0·27	6	100	Red cells ..	0	7·32	0·35	12	100
	10	1·87	0·13	5	33		1	4·70	0·10	12	64·2
	3	3·62	0·46	6	45·3		0·3	6·84	0·32	12	93·4
	1	6·11	0·56	6	76·6		0·1	6·82	0·29	12	93·1

*Schradan was given at 10, 3, and 1 p.p.m. for 13 weeks in Experiment 2 and at 1, 0·3, and 0·1 p.p.m. for four weeks in Experiment 3.
†ChE activity = Mean μl CO_2 evolved per minute per g. brain or ml. of blood.
** % activity = Activity expressed as percentage of control group.

one lasted for 13 and the other for only four weeks. There is some depression of the activity of cholinesterase at 1 p.p.m. more marked in the red cells than in the plasma.

"Systox."—Two experiments with "systox" were done on female rats only and ran for 16 weeks. The rats on 50 p.p.m. were the only ones to show signs of poisoning which were typically those produced by a cholinergic drug, namely, widespread fasciculations, weakness, and tremors with evidence of excessive lachrymation and salivation. After four weeks three rats in this group were killed because of the severity of their illness but the rest gradually recovered in spite of continued ingestion of the diet. The growth curves are given in Fig. 4 and show that only those rats on 50 p.p.m. were affected.

There were no incidental deaths in these experiments, and no deaths from specific poisoning other than the three rats that were deliberately killed.

The daily food intake of the rats was measured throughout the experiments and the data for the rats on 50, 20, and 10 p.p.m. are given in Fig. 5. There are no differences between rats on 10 p.p.m. and the controls. At 20 p.p.m. growth was similar but food intake somewhat greater for several weeks. At 50 p.p.m. food intake was low for the first four weeks while the rats were obviously very ill but it then increased and remained very high for six weeks. The relationship between food intake and growth is shown in Fig. 6 where data for the controls and the 50 p.p.m. group are plotted. In spite of the high food intake the rats on 50 p.p.m. "systox" remained lighter than the control rats throughout the experiment (Table 5).

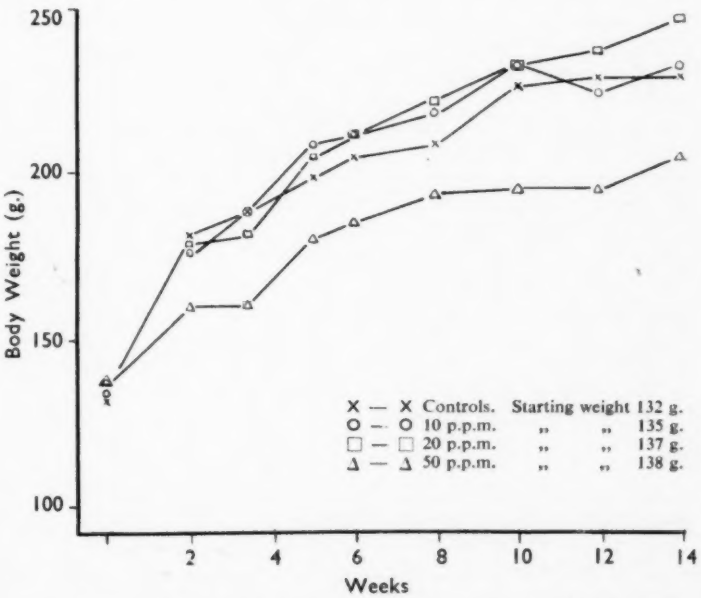


FIG. 4.—Weights of female rats on diets containing "systox" (Experiment 3).

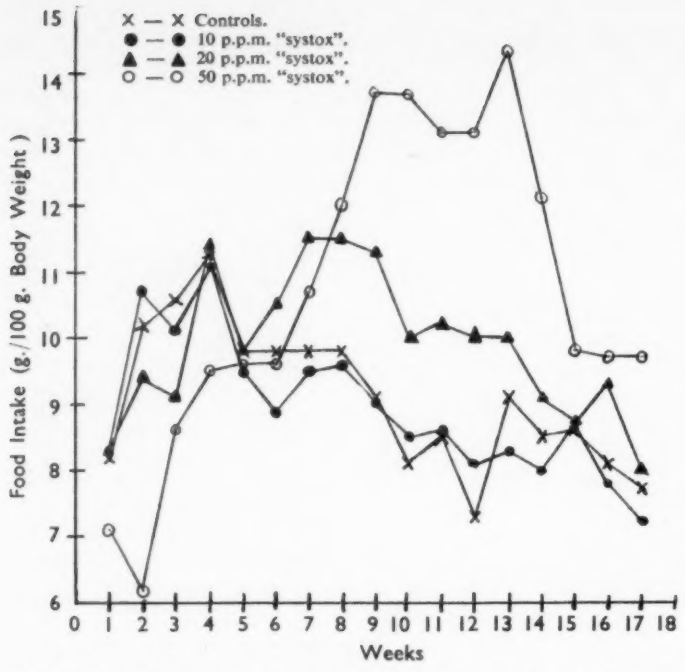


FIG. 5.—The daily food intake of rats on diets containing "systox". Each point is the mean daily intake for a week expressed as g. of dry diet per 100 g. body weight.

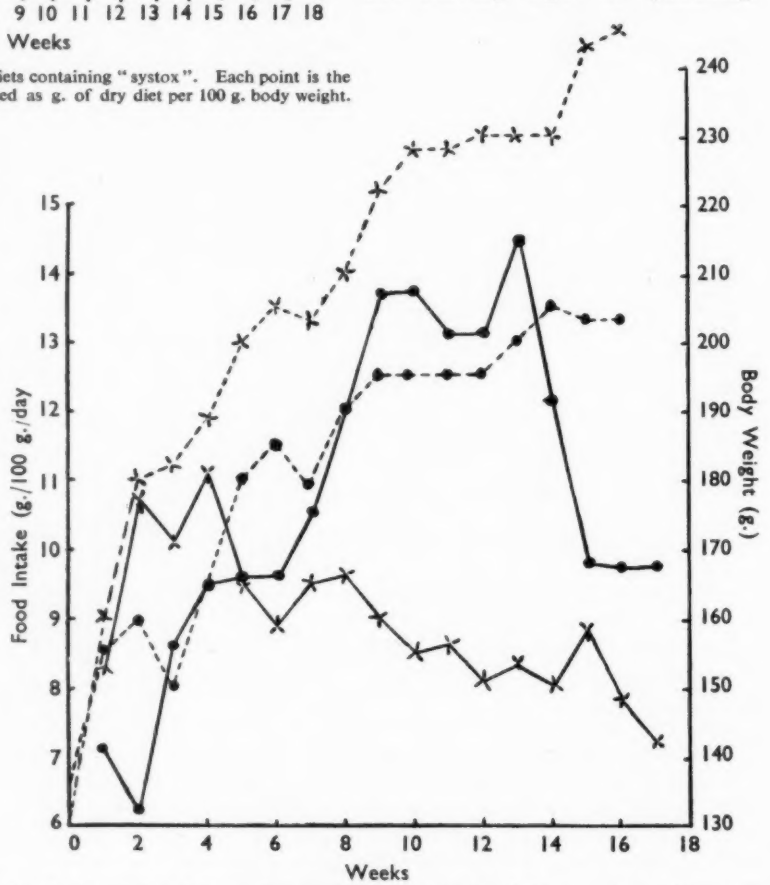
At 1 p.p.m. there is a detectable depression of both blood and brain cholinesterase. At 3 p.p.m. there is a reduction of the brain cholinesterase activity as great as that produced by 50 p.p.m. schradan (Table 3). At 20 p.p.m. there is a reduction of activity of over 80% of the brain cholinesterase in rats that were otherwise apparently normal. The rats on 50 p.p.m., because of their greater food intake, were consuming a dose of "systox" about three times greater than those on 20 p.p.m. but the inhibition of their brain cholinesterase only increased by another 6%. Nevertheless at the time this experiment ended the rats on 50 p.p.m. with only 7% of their brain cholinesterase were not showing signs of poisoning.

Although they started later and never reached the same final weight, the rate of growth of the rats on 50 p.p.m. "systox" was similar to that of the controls.

It was also surprising that the signs of poisoning diminished despite the increased intake of "systox" after the fourth week. The average daily intake of "systox" at different times during the experiment is given in Table 6.

At the fourth week the rats on 50 p.p.m. were consuming 70% of a single lethal dose and at nine weeks the equivalent of a single lethal dose each day.

The values for blood and brain cholinesterase are given in Table 7.



(*a*) × — × Food intake g./100 g. body weight per day.
× --- × Mean body weight (g.)
(*b*) ● — ● Food intake
● --- ● Mean body weight.

FIG. 6.—Comparison between the growth and food intake of (*a*) normal rats (*b*) rats on 50 p.p.m. "systox" in the diet.

TABLE 5

MEAN WEIGHTS OF FEMALE RATS RECEIVING 50 P.P.M. "SYSTOX" COMPARED WITH CONTROL RATS AT DIFFERENT TIME IN EXPERIMENT 4

Duration of Experiment (weeks)	Weight of Rats (g.)		t	p
	Control	50 p.p.m. Systox		
	Mean and S.D.	Mean and S.D.		
2	180 ± 15	160 ± 18	4·08	<0·01
7	201 ± 15	181 ± 11	3·25	<0·01
12	230 ± 18	197 ± 12	4·52	<0·01

TABLE 6

DAILY INTAKE OF "SYSTOX" CALCULATED FROM AVERAGE DAILY FOOD INTAKE IN EXPERIMENT 4

Level in Diet (p.p.m.)	Average Daily Intake per Rat (mg./kg.)		
	4th week	9th week	14th week
50	2·8	4·1	3·6
20	1·3	1·3	1·1

Despite their lowered cholinesterase activity they were able to consume daily a dose of "systox" equivalent to 96% of a single lethal dose for a normal rat.

Discussion

The experiments with the higher doses of schradan and "systox" were designed along the conventional lines of tests for chronic toxicity. The usual criteria for such tests are non-specific such as death, failure to grow, or loss of weight, and changes in behaviour, i.e., signs of poisoning followed by a macroscopical and microscopical examination of the tissues of animals killed or dying during the experiments. A failure to grow normally and a few mild signs of poisoning were seen in the male but not in the female rats receiving 50 p.p.m. schradan. In those male rats receiving 10 p.p.m. there were no signs of poisoning. More severe signs of poisoning and a similar disturbance of growth were seen in the female rats on 50 p.p.m. "systox" but on 20 p.p.m. "systox" the rats behaved normally. No rats developed pathological changes in the tissues as a result of ingesting these insecticides at the highest levels used.

By the ordinary standards of a toxicity test 50 p.p.m. schradan and 20 p.p.m. "systox" were harmless to female rats. Both these compounds have at least one specific action, namely the power to inhibit cholinesterase after they have been ingested by the animal. Using this specific test it was found that both compounds were having an effect at dietary levels considerably below those producing other signs of intoxication. Thus, at 3 p.p.m. both produced a 30% inhibition of the blood cholinesterase activity and it is probable that a slight effect was produced even at 1 p.p.m. On the other hand, rats on 20 p.p.m. "systox" behaved apparently normally even though their brain cholinesterase activity had been 85% inhibited. If such a diet can be consumed without obvious signs of poisoning should a diet be considered "toxic" that will produce a depression of cholinesterase activity of 5 to 10%?

TABLE 7

CHOLINESTERASE ACTIVITY OF BRAIN, WHOLE BLOOD, PLASMA, AND RED CELLS OF FEMALE RATS FED DIETS CONTAINING "SYSTOX"

Experiment 4*						Experiment 5*					
	Drug in Diet (p.p.m.)	†ChE Activity	S.E.	No. of Rats	% **Activity		Drug in Diet (p.p.m.)	ChE Activity	S.E.	No. of Rats	% Activity
Brain	0	175	7·56	12	100	Brain	0	209·7	10·12	7	100
	10	46	2·88	12	26·5		10	42·1	1·13	8	20·1
	20	22·95	3·81	12	13·1		3	138·2	4·44	7	66·0
	50	13·66	3·40	12	7·1		1	194·2	6·90	7	93·0
Whole blood	0	28·87	1·805	12	100	Whole blood	0	27·63	1·71	7	100
	10	8·21	0·69	12	28·4		10	5·89	0·42	8	21·2
	20	4·25	0·67	12	14·8		3	19·06	1·07	7	69·0
	50	2·40	0·83	12	8·2		1	24·92	1·29	7	90·0
						Plasma	0	24·49	2·65	7	100
							10	6·57	0·57	8	26·8
							3	17·17	1·61	7	70·0
							1	23·39	1·72	7	95·5
						Red cells	0	7·50	0·70	7	100
							10	1·18	0·23	8	15·8
							3	5·96	0·85	7	80
							1	6·19	0·98	7	83

*In experiment 4, 50, 20, 10 p.p.m. "systox" was given for 16 weeks, and in Experiment 5, 10, 3, and 1 p.p.m. "systox" for 11 weeks.
† ChE activity = Mean μl. CO_2 evolved per minute per g. brain or ml. of blood.
** % activity = Activity expressed as percentage of control group.

The two compounds exhibit some differences in their behaviour as inhibitors of cholinesterase in the rat. "Systox" always produces a greater degree of inhibition of the brain cholinesterase than schradan. Their effect upon the whole blood is similar but schradan consistently produces slightly more inhibition of the cholinesterase of the red cells than the cholinesterase of the plasma. It might seem reasonable to conclude that "systox" was more toxic than schradan at similar levels in the diet because it produced a greater effect upon the brain cholinesterase. Before reaching this conclusion it would be more satisfactory if we knew whether the inhibition of cholinesterase was the sole toxic action of these compounds and also more about the function of cholinesterase.

The rats on 50 p.p.m. "systox" were very ill for several weeks and then began to recover. By the end of the experiment signs of poisoning had disappeared but their brain and blood cholinesterase activity was only 7 to 8% of normal. The toxicity of an inhibitor of cholinesterase given in repeated doses will be determined to some extent by the rate at which inhibition of the cholinesterase is reversed. The mechanism of inhibition and its reversal have been studied in some detail (Aldridge, 1953b) and the rate of reversal of inhibition by organophosphorus compounds is determined by the nature of the alkoxy groups attached to the phosphorus (Aldridge and Davison, 1953). Unpublished observations in this laboratory by Davison have shown that with one inhibitor at least the speed with which the inhibition of cholinesterase is reversed in the rat is the same after a comparable degree of inhibition produced in one case by a single dose and maintained in the other continuously for six months by feeding. It seems unlikely that the tolerance developed by the rats to 50 p.p.m. "systox" was associated with any increase in the speed with which the inhibition of cholinesterase could be reversed. In any case, the extent to which this had taken place by the end of the experimental period was very small.

Observations of a different type have shown that adequate function of the myoneural junction of the rat may be maintained when only 10% of the normal activity of cholinesterase remains although disturbances in function may be produced while the inhibition is progressing (Barnes and Duff, 1953). It seems, therefore, more probable that the rats on 50 p.p.m. "systox" in some way adjusted themselves to an existence with only 7 to 8% of their normal quota of active cholinesterase.

Associated with this severe depression of cholinesterase activity there was a disturbance in growth and a defect in the body weight persisting throughout the experiment. But for the last eight weeks this defect in growth was associated with an abnormally large food intake (Fig. 5). This demand for more food may be part of the adjustment of the animal to serious defects in its tissue cholinesterase levels. If this is so, it implies that cholinesterase has functions not yet recognized. The increased intake of food might be for quite different reasons and perhaps related to poor utilization of the food ingested. There might be an increased mobility of the gut due to overaction of acetylcholine causing a too rapid passage of food. Digestion might be disturbed by the action of "systox" on other enzymes in the gut. Esterases other than cholinesterases (Aldridge, 1953a) as well as chymotrypsin (Hartley and Kilby, 1952) are very sensitive to these organo-phosphorus compounds. An answer to this question might well throw more light on the action of "systox" and related anti-cholinesterases.

The defect in growth of the male rats on 50 p.p.m. schradan was not associated with a reduction of the tissue cholinesterase activity as marked as that of the rats (female) on 20 p.p.m. "systox" which grew normally. Female rats of 50 p.p.m. schradan had a similar degree of inhibition to that produced in the males but they grew normally. The growth of male rats may be more sensitive than that of females to a depression of cholinesterase activity or schradan may interfere with growth by another mechanism. The failure of male rats on schradan to grow properly was not associated with any alteration in the food intake. In the rat schradan is converted into an inhibitor of cholinesterase in the liver. Neither male nor female rats show any histological changes in the liver as a result of this, but it is conceivable that this process of chemical transformation of schradan might interfere with a factor more important to the growth of male than of female rats.

It is difficult to use these experiments to make a comparison between the toxicity of "systox" and schradan. For female rats "systox" is more poisonous than schradan at a level of 50 p.p.m. and at lower levels it produces more inhibition of the brain cholinesterase than does schradan. Little is known of the factors that determine the degree of inhibition produced in different tissues by different inhibitors of this group. Nor is it known what part selectivity in the site of action plays in determining the toxicity of a given inhibitor of cholinesterase. While the importance of cholinesterase in the nervous system would appear to be outstanding less is known about the function of this enzyme at other sites including, for example, the red blood cells. The action of schradan on the growth of male rats

suggests an action of this compound possibly unrelated to that on cholinesterase and this might be of equal or greater importance if more was known about it.

The significance of a small (10%) depression of cholinesterase activity remains unknown. So little is known about the specific actions of other toxic substances in the whole animal that it is not possible to say at present whether it is usual for signs of intoxication to appear only when 90% of some enzyme activity has been inhibited or whether it is more usual for such signs to appear after smaller depressions of some specific activity.

The value of toxicity tests and their interpretation will be improved only when more information along such lines has been acquired.

Summary

Rats have been given diets containing 50, 10, 3, 1, 0·3, and 0·1 p.p.m. schradan (octamethyl pyrophosphoramide) and 50, 20, 10, 3, and 1 p.p.m. "systox" (OO-diethyl-S-ethyl thioethanol thiophosphate).

Signs of poisoning and diminished growth were found in male but not female rats at 50 p.p.m. schradan. "Systox" was given only to female rats and those receiving 50 p.p.m. showed signs of poisoning and did not grow as well as the controls.

Rats on 20 p.p.m. "systox" appeared normal although the activity of the cholinesterase of their blood and brain was only about 15% of normal.

"Systox" affected the blood and brain cholinesterase equally and had a similar activity toward the true and pseudo-cholinesterase of the rat. Schradan affected the blood more than the brain and preferentially attacked true rather than pseudo-cholinesterase.

Signs of poisoning in animals receiving 50 p.p.m. "systox" became very severe after three to four weeks but gradually decreased despite continued feeding. An initially low food intake became much greater than that of the control rats for the later part of the experiment. Blood and brain cholinesterase activities were inhibited to 95% of normal.

Schradan at 50 p.p.m. had a less serious effect on the cholinesterase even in the rats where growth was depressed. The food intake of these rats was normal.

Some inhibition was seen in rats fed 3 p.p.m. of either "systox" or schradan and a slight effect was recorded even at 1 p.p.m.

No histological changes were observed in the rats on the highest doses of schradan or "systox".

The findings are discussed and reference made to the difficulties of interpreting tests for chronic toxicity.

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Mr. C. R. Kennedy was responsible for the running and the records of the feeding experiments and Mrs. Kemp and Mr. A. Batchelor for the cholinesterase determinations.

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SICKNESS ABSENCE BEFORE THE FIRST CLINICAL EPISODE OF CORONARY HEART DISEASE

BY

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There is a common belief that coronary (ischaemic) heart disease strikes healthy people without warning, and that it is related to personality (Dunbar, 1948); for example, the over-conscientious or the ambitious man. For these reasons, and in order to look for possible indications of future coronary disease, we took the opportunity while working with the records of London Transport Executive employees (Morris, Heady, Raffle, Roberts, and Parks, 1953) to compare the previous sickness experience of men suffering from a first clinical episode of coronary heart disease with the experience of other men chosen as controls. The idea was to make a preliminary examination, using data which would be sufficient to demonstrate a striking difference, though possibly not numerous enough to show a small one. With the material and methods at our disposal we felt that only a large difference would be worth following up.

Material and Methods

The investigation was restricted to drivers and male conductors of the central (red) buses aged between 44 and 64 inclusive, of whom there were approximately 16,000 in 1949. The plan was to choose four "controls" for each "case". The "cases", as said, comprised all the men in the investigation who had a first clinical attack of coronary heart disease in 1949, whatever clinical form this took, whether as angina pectoris or as a "coronary thrombosis" (myocardial infarction). The controls were to be men without any record of coronary heart disease: some might be suffering at the time or have suffered in the past from other form of illness, but in practice the great majority would not be sick men. All cases and controls were on the "active list" of employees at the date on which the onset of the coronary episode brought men into the inquiry.

As the population from which the controls were drawn was so large, we were able to take account of five factors which might otherwise have biased the comparisons. These factors, for which cases and controls were matched, were: (1) Sex: the investigation was restricted to males only. (2) Age: the cases and controls were born in the same year. (3) Occupation: drivers were compared with drivers, and conductors with conductors. (4) Length of service with London Transport or the transport undertakings which preceded it: the cases and controls started service in the same year. (5) Group of garages: in 1949 the garages in the central area of London (which actually includes some of the suburbs) were grouped in three divisions. Cases and controls were drawn from the same division.

Finding the Controls.—A Hollerith punched card was available for each of the drivers and conductors from whom the controls were drawn. The cards (which included details of the five factors mentioned above) were sorted into batches representing drivers and conductors separately for each of the three divisions, making six batches in all. Cards in each of these batches were next sorted according to the last two figures only of the five-figure badge number* and so placed in virtually random order. The cards were then sorted into years of birth and years of entry to service, and lists were made of the cards in each sub-category so formed. The cases were similarly sorted and listed by division, occupation, year of birth, and year of entry to service.

Next, a clerk took the first man on the list of cases and looked through the list of possible controls until he found the first four men in the same occupation and geographical division with the same year of birth and year of entry to service. If it was not possible to select four controls with these characteristics the process was repeated for years of birth, and/or years of entry, which differed by one from the index year. No further substitution was

* The five-figure badge number is the serial number of the public service vehicle licence issued individually to the driver or conductor by the metropolitan police.

permitted. In all, 137 controls were listed for 36 cases. A further scrutiny of the data revealed that a few cases had changed their occupation from conductor to driver, or vice versa. These cases were excluded, together with all their controls. Any controls who had changed their occupations were also discarded. This left 31 cases and 101 controls matched for the original five factors together, now, with a sixth—length of service in a particular occupation.

The Record of Sickness.—The individual staff record for each of these men was available and included details of employment and all absence due to sickness or accident experienced by the man concerned (Spratling and Lloyd, 1951). The record of absences also included annual and other leave thus making it possible to tell in which year the record actually started. This was not always the year of entry to the service ; but cases and controls were compared only for the period where the recording was complete. This period averaged 22 years. The end-point of the period of comparison for each control was the date of the corresponding case's first absence from work for coronary heart disease. We allowed for gaps in the records during war service by an arbitrary method ; only 12 individuals were affected, four cases and eight controls. Length of absence is recorded in days, including the first day of absence but not the day of return, and we made no attempt to exclude Sundays, or bank holidays, or rest days which fell within the period of absence. We treated absences with no record of an end date as if they were for a single day. This again was an arbitrary procedure, justified by internal evidence and by the experience of the administrative staff. In any event very few absences were affected and both cases and controls were treated alike.

Because we included in our analysis only absences recorded as due to sickness or accident, " special " leave (e.g. for compassionate reasons) and absences without leave were excluded. It is possible that some short absences of one or two days, recorded as absence without leave, may have been due to sickness, or vice versa. A check made for the years 1951 and 1952 showed that the total number of days of absence without leave for drivers and conductors averaged only about one twentieth of the number of days of absence due to sickness. Pre-war records are not available but it is understood that there was even less absence without leave before the war. Not only is the extent of the absence without leave relatively unimportant compared with sickness absence, but there is no reason to believe that cases and controls differ in this respect.

We made little use of the recorded diagnosis of the cause of absence, because of the small numbers in the trial, frequent vagueness of recorded causes, and occasional omissions. The diagnosis was, however, used to separate absences due to injury ; and the records were also scrutinized for evidence of hypertension, diabetes, and other conditions possibly related to coronary heart disease.

We examined the individual staff records for both sickness absence and absence due to injury in two only out of the three divisions of garages, the numbers available being 23 cases and 77 controls—100 men in all. These 100 men represent, in total, 2,195 years of experience and they were absent from work on account of sickness or accident 1,089 times for a total of 21,949 days. As it happens, therefore, each man was absent, on an average, about 11 times, and lost on the average 10 days each year, (including, as mentioned earlier, Sundays, public holidays, and rest days if they fell in the period of absence). We examined the records of the third division of garages for injuries only. Injuries are therefore dealt with separately, the number of men concerned being 132—all the 31 cases and 101 controls.

Classification of Absences.—We have classified absences according to their length as follows : " Short " absences (three days or less), " medium " absences (4–13 days inclusive), " medium long " absences (14–60 days inclusive), and " long " absences (61 days or more). In addition, as stated, we analysed separately absences due to injury, where the cause, as recorded, was traumatic. Within all these categories, for absences due to sickness, we compared the cases and controls according to both (*a*) the number of absences and (*b*) the total number of days of absence. For absences due to injury, we considered only the number of absences. In all the comparisons the main purpose, which was aided by the design of the trial, was to compare the history of the cases and controls, excluding as many confounding factors as possible. The factors excluded were of course those for which the cases and controls were matched : importantly sex, age, and length of service in a particular job.

Results

The results for the cases and the controls are compared in Tables 1 and 2.

Number of Absences.—Table 1 deals with the number of times the " average man " in each

TABLE 1

PREVIOUS SICKNESS ABSENCE OF MEN WITH FIRST CLINICAL EPISODES OF CORONARY HEART DISEASE COMPARED WITH CONTROLS

Type of Absence	Average Number of Absences per Man		Average Number of Days Absent per Man	
	23 Men with Coronary Heart Disease	77 Controls	23 Men with Coronary Heart Disease	77 Controls
Short 1–3 days inclusive	2·1 (±0·64)	1·5 (±0·21)	3 (±0·8)	2 (±0·3)
Medium 4–13 days inclusive	4·0 (±0·83)	4·0 (±0·43)	38 (±8·1)	35 (±3·5)
Medium long 14-60 days inclusive	5·3 (±0·97)	3·9 (±0·46)	131 (±23·8)	93 (±10·7)
Long 61 days or more ..	0·8 (±0·27)	0·6 (±0·12)	76 (±27·2)	65 (±14·8)
All absences ..	12·3 (±1·75)	10·1 (±0·75)	248 (±44·9)	195 (±20·8)

The first clinical episode of coronary heart disease occurred in 1949. The previous experience of absence goes back as far as the records allow, on an average, 22 years. The men were aged 44–64 in 1949. There were not always the same number of controls for each man with coronary heart disease; the averages presented for the controls are therefore averages of the means for each group of controls.

The figures in brackets preceded by the ± sign are the standard errors of the averages shown above them. No individual difference is significant at the 5% level. In addition, the analysis of variance was used to test the differences for all absences, for "short" absences, for all absences other than "short," for "long" absences, and for absences due to injury, both as regards the number of sickness absences and the number of days absent, except that for short absences and absences due to injury there was no such analysis for the number of days absent. The test which allows for differences between drivers and conductors, and eliminates from the comparison the other factors used in the matching process, showed no significant difference between men with coronary heart disease and controls.

group was absent during the period of comparison, and breaks this number down into the different types of absence, classified as we have just described according to the length of the absence.

Number of Days Absent.—Table 1 shows also the number of days the average man in each group lost through sickness during the period of comparison, and breaks this number down in a similar way.

The men with coronary heart disease show an excess of two absences and just over 50 days of absence per man in a mean experience of 22 years. They have an excess in each type of absence (except in absences of four to 13 days when they are equal) but it will be noted that the standard errors of the averages are large in comparison with these differences and no difference is significant at the conventional 5% level.

Differences in Distribution of Absences.—It is possible that the averages shown above are obscuring important points. Although the averages are not significantly different there might, for instance, be considerably more variation in the number of absences amongst the controls than amongst the cases. This might result, for example, in a much higher proportion of men with no absences and with many absences in the cases, but more with a moderate number of absences in the controls. Table 2 shows that, while there may be differences of this sort, consistent with the general pattern of more absence amongst the cases than among the controls, such differences cannot be conclusively demonstrated because none of those shown in the Table are significant at the 5% level. It is possible that real differences exist, but as before, are too small to be demonstrable in a sample of this size.

These three measures—the number of absences, the number of days absent, and the distribution of the number of absences—summarize most of the information which can be extracted from the present type of analysis.

TABLE 2

PREVIOUS SICKNESS ABSENCE OF MEN WITH FIRST CLINICAL EPISODES OF CORONARY HEART DISEASE COMPARED WITH CONTROLS

Percentage of Men with	23 Men with Coronary Heart Disease	Among 77 Controls
Less than 5 absences of all durations	17%	26%
More than 20 ,, ,, ,, ,,	22	12
No "short" absences	43	36
No "long" absences	52	60

None of these differences is significant at the 5% level. See also notes to Table 1.

Absences Due to Injury.—The mean number of absences per man due to injury during the whole period of observation was 1·0 among the cases and 0·7 among the controls. This difference also, although in the same direction as before, is not significant at the 5% level.

Other Comparisons.—There were no significant differences between drivers and conductors, either amongst the cases or amongst the controls, and they are therefore not shown separately in the table. Similarly, there were no differences between divisions of garages. The number of absences increased, of course, with age and length of service.

Comment

There is no striking difference between the experience of cases and controls, though there may possibly be small differences.

A negative result of this sort—the absence of a significant numerical difference or of a difference in pattern—is difficult to interpret. To have found a

difference would have been interesting ; to demonstrate that there is *no* difference would be at least as interesting. But unfortunately, a limited trial such as this cannot possibly *prove* the absence of a difference. It may be that there is a difference, but in other characteristics than those we have examined, for instance, in connexion with the diagnosis of the cause of sickness absence, or between the previous experience of cases who died " suddenly " in their first clinical attack of coronary heart disease and those who did not. To test this last possibility would require far larger numbers than we have at our disposal. We cannot think of other useful ways in which these sickness data could have been analysed in quantitative terms, but that does not mean that there are none. Moreover, it is possible that there is a difference, even in the characteristics we have examined, which is too small to be shown in the limited experience presented. In this connexion it is important that the differences, though not significant, show a consistent slight excess of absence amongst the cases. But it should not be forgotten that the three measures, " number of absences per man ", " number of days absent per man " (Table 1), and the distribution of absences (Table 2), are in a very real sense only different ways of presenting the same material. If there were a real difference in, say, the number of absences, it would almost certainly show up also in the number of days absent and in the " distribution " table. In other words, these three pieces of evidence must not be accepted as independent. Further, we are dealing throughout with the same 100 men and it is quite possible that, for instance, a man who is more likely than his fellows to have absences of, say, 14 to 60 days is also more likely to have absences of four to 13 days, or for more than 60 days. The choice of the number of days of absence for the analysis of different types of absence is quite arbitrary. We may be dealing *by chance* with a slightly more sickly group of men in the cases than in the controls, because the controls, as we have shown, were drawn as nearly as possible at random. Even if we assume that the numbers of absences of different lengths are independent, and calculate the probability that differences of the observed sizes will all fall the same way, the result is still quite likely to have occurred by chance, the calculated probability of this chance being greater than the conventional 5%. Moreover, the degree of apparent consistency seen in Tables 1 and 2 in the difference between cases and controls disappears when drivers and conductors are analysed separately.

There is another aspect to these figures. Detailed analysis of the data (which we have not the space to show) indicates very clearly that the variation among individual men is consistently greater than between the two groups, cases and controls. Individual differences are in fact very great. The conventional measure of this variability, the standard deviation of the number of absences of all types (as opposed to the standard error of the average shown in Table 1) amongst cases and controls is 7·4.

The important point is that, even if there is a real group difference (cases as against controls) it cannot be large compared with the individual differences. It can be shown, using the numbers in Table 1, that the difference between the mean number of absences per man in the two groups is unlikely to be greater than four in 22 years of comparison. For this reason the approach through the study of sickness absence is unlikely to have any prognostic value in picking out men who are particularly susceptible to coronary heart disease.*

Since the results give no indication of a striking difference, which alone would be interesting with this type of material, no further extension of the present pilot study is felt to be justified. The small differences shown in this paper would only have been significant at the 5% level if there had been four times as many cases and controls.

Conclusion

There is no suggestion that there is any important difference in the health history, as here examined, of the cases and the controls, in particular of a difference which might be associated with a characteristic type of personality. To some extent, however, the result can be looked on as support for the idea mentioned earlier that coronary heart disease strikes suddenly and without warning, though not that coronary heart disease selects particularly healthy men. Taken at their face value, the present observations suggest that the previous sickness absence of cases of coronary heart disease presenting for the first time is, on the average, similar to that of any group of comparable men still in active work. There is little in their previous sickness record to distinguish the coronary cases from their normal fellows who do not suffer from coronary heart disease. If anything there is a slight indication that men with coronary heart disease have more sickness than these " normals ", rather than less. Amongst any such " normal " group there will be people with good and bad health records, including the man with an absolutely clear record. This variation in health record is also characteristic of men who

* An examination of the records of the cases shows no absence at all before the first clinical attack of coronary heart disease for related conditions such as hypertension and diabetes, so that the slight overall excess found in the cases cannot be explained in this way.

eventually get coronary heart disease, and is much greater in the present material than the variation between men who are going to get the disease and those who are not. It would be interesting to carry out a similar trial for men suffering from other common diseases of middle-age, duodenal ulcer and cancer, for instance. Many such problems of the previous history of men with different complaints, or of the association and dissociation of various diseases, could be investigated from the statistics collected day by day in industry where, moreover, the difficult problem of the selection of adequate " controls " may often be readily resolved.

Summary

The sickness absence experience before the onset of the first clinical episode of coronary heart disease in a group of drivers and male conductors of the London Transport Executive is compared with that of a group of controls matched for sex, age, job, and length of service. No significant differences at the 5% level are found between the two groups, either in the number of absences, the total number of days of absence, or in the distribution of different types of absences.

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PILOT TRIAL OF AN ANTIHISTAMINIC DRUG IN THE CONTROL OF "TETRYL" DERMATITIS

BY

W. A. BAIN and GRIZEL H. THOMSON

From the Department of Pharmacology, University of Leeds, and a Royal Ordnance Factory

(RECEIVED FOR PUBLICATION OCTOBER 5, 1952)

The compound 2 : 4 : 6 trinitrophenylmethylnitramine, known commercially as " tetryl " and in the Services as C.E. (Composition Exploding), is an important intermediate detonating agent for high explosive charges. It has long been known that workers with " tetryl ", in addition to becoming yellow about the hands and face, are prone to develop dermatitis and respiratory troubles (Smith, 1916; Cripps, 1917; Ruxton, 1917). When contact with " tetryl " is heavy and workers are new to the job the incidence of dermatitis is high, however carefully the workers are selected, and however stringent the application of preventive measures, such as protective clothing, barrier creams, and the like. Of new people who go into training for work in heavy contact with " tetryl " only a few complete the course and many of these leave work at the first onset of symptoms, or even from fear of the substance and what it may do to them.

Heavy contact is suffered by those who press " tetryl " into pellets. The labour problem presented by this type of work is illustrated by Table 1, which shows the turnover of trained pressworkers in an 11-month-period, together with an analysis of the reasons for the high rate of loss.

TABLE 1
LABOUR TURNOVER OF "TETRYL" PRESSWORKERS IN 11 MONTHS

Total trained and entering presswork	47
Number on presswork at end of period	5
Number lost to presswork by end of period	42
Reasons for Loss of Pressworkers	
Personal : incipient dermatitis ; fear of ill-health, including dermatitis ; staining of skin ; other factors	25
Medical : removed from presswork by Medical Officer for dermatitis (10) or other medical reasons (3).. ..	13
Production : transferred by Production Department to other work	4
	42

It is clear from Table 1 that, apart from transfers to other jobs by the Production Department, workers lost to the presses fall into two main categories. In the first are those who leave, often on very slight provocation, for personal reasons—because of staining of the skin and clothing, the fear of skin trouble, the onset of symptoms of skin trouble, the respiratory irritation caused by " tetryl " dust, and other factors. These are the people who will not tolerate in peace time the discomforts that they might endure or ignore in time of war. In the second category are those willing to suffer discomfort, often of considerable degree, and who are only removed from heavy contact on the direction of the medical officer.

This high wastage of labour makes it difficult to maintain an adequate number of pressworkers. Any safe and effective means of treating or preventing the skin condition would not only reduce the losses from dermatitis itself but would be likely to lessen or abolish the fear of it and thus lower the losses from personal reasons.

Without going into detail it may be said that the dermatitis develops after eight to 15 days' contact with " tetryl ", and that people who have recovered from an attack can often return to a lesser, or less commonly to the same, degree of contact, without developing further symptoms. Such are said to have been " salted ". Those who do not develop dermatitis at all, some 10% or less of those in heavy contact, are said to be " naturally immune " or " naturally salted".

Theoretical Basis of Trial

As the premonitory symptoms are usually either itching of the face and neck, progressing to erythema and urticaria, or rhinitis with respiratory discomfort suggestive of mild asthma, it looked as if the onset of the condition was associated with the release of histamine. The fully developed dermatitis

eventually get coronary heart disease, and is much greater in the present material than the variation between men who are going to get the disease and those who are not. It would be interesting to carry out a similar trial for men suffering from other common diseases of middle-age, duodenal ulcer and cancer, for instance. Many such problems of the previous history of men with different complaints, or of the association and dissociation of various diseases, could be investigated from the statistics collected day by day in industry where, moreover, the difficult problem of the selection of adequate " controls " may often be readily resolved.

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Theoretical Basis of Trial

As the premonitory symptoms are usually either itching of the face and neck, progressing to erythema and urticaria, or rhinitis with respiratory discomfort suggestive of mild asthma, it looked as if the onset of the condition was associated with the release of histamine. The fully developed dermatitis

might thus be the end-result of a process in which such release played an important part. The histamine release might result either from a sensitization reaction to " tetryl ", such as has been suggested by Gell (1944), or from " tetryl " acting as a simple histamine liberator. In either event it seemed possible that if adequate doses of a suitable antihistaminic drug were given by mouth at a sufficiently early stage the symptoms or signs might be modified or suppressed and " salting " occur, whether due to desensitization in the strict sense or to depletion of skin histamine or both, without the development of a frank and disabling dermatitis.

In view of the accident risk in work with " tetryl ", and the known side-effects of antihistaminics that might well aggravate this, it was clear that before any large-scale controlled trial could be justified a preliminary or pilot trial would have to be conducted, in which the medical officer in charge knew exactly what was being given and in what dose, and could be on the look-out for the sort of actions that might lower the standard of safety precautions. A pilot trial of this kind would show not only whether a large-scale rigorous trial was likely to be worth while, but would also provide information of various kinds that would be useful in the design and conduct of a rigorous trial, such as, for example, those drugs and their doses likely to be both safe and effective ; the most satisfactory stage at which to begin therapy ; how long treatment should continue ; and so on. It is such a pilot trial, conducted under the only conditions open to us, that is described here in the belief that it affords a case for a larger scale trial.

Plan and Conduct of Trial

For reasons that need not be detailed it was not possible to have as control subjects people who were merely given dummy tablets. The only controls, therefore, were people treated by orthodox (" standard ") methods, some at the beginning of the trial period, some in the middle, and some towards the end. Furthermore, as workers could not be compelled to take drugs, random allocation of subjects to experimental and standard treatments was not feasible. These defects in the trial were unavoidable. Much was already known, however, about the results of standard treatment, and we therefore considered that any improvement shown by the new treatment over the old, dramatic enough to justify our suggesting that the matter be further pursued, would be sufficiently evident even under these restricted conditions.

A further defect of the trial, but a necessary one in view of the information sought, was that the experimental treatment was started at various stages in different groups of subjects—sometimes when dermatitis was evident and even severe, and sometimes when only itching or erythema was present. In the analysis of the results these differences have been ignored, though the results themselves made it evident, as was to be expected, that the earlier treatment was started the better.

A careful and full record of the history and progress of each subject was kept by recording daily all information that could conceivably be relevant to the assessment and interpretation of the results. The collection of this information by the medical and the training or production staff was an onerous task ; but, since no indication of how the data would be treated was divulged until after the end of the trial, there was thus introduced into the final grouping of results an element of objectivity that might otherwise have been lacking. Though the records of the trial are complex, its aim was simple : the results are therefore presented in a general and simple way.

On all grounds it seemed desirable to use a powerful and long-acting drug in doses as low as were likely to be effective. A single dose at night was regarded as the ideal, with, if necessary, a smaller " boosting " dose of the same drug in the morning. In this way the maximum antihistaminic level would be reached during the night, and side-effects be absent or minimal the next day (Bain, Broadbent, and Warin, 1949). But should the antihistaminic effect fall too low during the day it would be maintained by the smaller morning dose, which would be unlikely, by itself, to produce side-effects.

Two drugs with the necessary potencies and durations of action were available, promethazine hydrochloride B.P. and chlorcyclizine hydrochloride A.N. (Bain, 1949, 1951). As in doses giving comparable antihistaminic effects promethazine is much more prone to produce sleepiness than chlorcyclizine, the latter was preferred for the trial. Chlorcyclizine is dl-l-(p-chlorobenzhydryl)-4-methylpiperazine monohydrochloride, and the preparation used was " histantin " (Burroughs Wellcome & Co.). The proposed dosage scheme was 50 mg. at night, followed, if necessary, by 25 mg. the following morning. In view of the known variation in the response to antihistaminics (Bain, Hellier, and Warin, 1948) it was appreciated that the doses used might have to be adjusted to individual needs. This was accordingly done when necessary, but only after it was clearly safe to do so. The average daily dose was, in fact, about 100 mg.—50 mg. night and

morning but one or two people were given as much as 275 mg. in one day. Some subjects probably did not take the full amount of the drug provided, and this may account for some of the failures in the trial.

The use of ephedrine or amphetamine sulphate to control drowsiness during the first day or two of antihistaminic treatment was regarded as an important safety precaution, especially in the early stages of the trial and in people who were given a full morning dose of the antihistamine. Though this constituted a further defect in the trial it was justified on the grounds of safety. It soon became evident that the incidence of drowsiness was negligible with the doses of antihistamine generally used; but the sympathomimetic drugs seemed more effective than the antihistaminic in controlling the respiratory symptoms sometimes associated with the dermatitis, and so were sometimes used, along with the antihistamine, mainly for this purpose.

Before detailing the results it is desirable to describe the standard treatment used in the control group. This was started as soon as symptoms or signs developed, but most people who required it had to be removed from contact with "tetryl", since otherwise the dermatitis progressed. Preparations for local application to the affected areas were given. For erythema, papular rashes, and all cases of oedema without vesiculation, this was a calamine and lead lotion:

Calamine lotion	96	
Strong solution of lead subacetate	4	

For all cases with exudation, or marked vesiculation, the use of this was preceded by the application of a lead, zinc, and starch lotion:

Strong solution of lead subacetate	5	
Zinc oxide	2	5
Starch	2	5
Glycerin	1	25
Water	to 100	

For subacute erythema, and during the recovery stage following the use of the calamine or starch lotion, a special calamine cream was used:

Calamine	3	5
Kaolin	8	
Glycerin	16	
Emulsifying wax	9	
Perfume	q. s.	
Solution of Bordeaux B.	q. s.	
Water	63	5

or a special oily calamine lotion:

Calamine	5	
Liquid paraffin	50	
Oleic acid		5
Wool fat	1	
Solution of calcium hydroxide to	100	

When sleep was disturbed by itching, phenobarbitone (65 mg.) was given at night.

Workers with very severe oedema, with or without vesiculation, were kept resting in the surgery, and the affected areas were treated first with saline compresses, and then with the calamine and lead, or the lead, zinc, and starch lotion.

These local applications were not withheld from patients in the antihistamine-treated group if they wished to use them, or if the medical officer thought their use in any particular instance was desirable. But nobody on antihistaminic treatment was given phenobarbitone.

Results

In the main part of the trial 28 patients had the antihistaminic treatment and 16 the "standard" treatment.

When a medical criterion of success or failure is used results are as shown in Table 2. The successes in this table are the people actually or potentially available for continued work in heavy contact with "tetryl". The failures are those who relapsed on return to presswork and so were removed from heavy contact by the medical officer. There were thus 26 successes out of 28 in the antihistamine-treated group, but only four out of 16 in the "standard" treatment group. Or, alternatively, of the 30 successes, 26 had received the new treatment and four the old, whereas of the 14 failures only two had received the new treatment and 12 the old. The probability that such differences would occur by chance, in a rigorous experiment with random allocation of subjects to control and experimental groups respectively, is less than 0·1%.

TABLE 2
RESULTS OF TREATMENT ASSESSED ON A MEDICAL CRITERION

	Antihistaminic Treatment	Standard Treatment
Successes*	26	4
Failures†	2	12

*Successes are people actually engaged on, or potentially available for, presswork after treatment.
†Failures are people who relapsed on return to presswork.

As the labour and production problem deriving from "tetryl" dermatitis or the fear of it is of fundamental importance, it was of interest to assess the results entirely on a labour and production criterion. This is done in Table 3 in which the first row of the preceding table is modified by the subtraction of losses for personal or production reasons, or for medical reasons other than "tetryl" dermatitis, and so includes only those in each treatment group who continued to work as pressmen. The lower row remains unchanged as it includes only

TABLE 3
RESULTS OF TREATMENT ASSESSED ON A PRODUCTION CRITERION

	Antihistaminic Treatment	Standard Treatment
Continuing work as pressmen	20	2
Unable to continue work as pressmen	2	12

the medical failures who, by definition, could not continue to act as pressmen. Thus of 22 men continuing at work on the presses, 20 had received the new treatment and two the old, whereas of 14 who could not be maintained at this work, only two had received the new treatment and 12 the old. As before, the probability of such differences arising by chance in a rigorous experiment is less than 0·1%.

Twenty further patients were treated with chlorcyclizine subsequent to the trial period proper. Three of these were failures. If these 20 results are added to the first column of Table 2 the figures there become 43 and 5 respectively. These 48 people will be referred to later.

Though the aim of the pilot trial was to get evidence that would show whether a rigorous trial was likely to be worth while, the results set forth in Tables 2 and 3 might seem so overwhelmingly in favour of the antihistaminic therapy as to make any further trial superfluous. But it must be stressed that the pilot trial suffered by its very nature, and by some of the conditions and limitations necessarily imposed upon it, from defects of design and conduct such as would make it unjustifiable to attribute the observed differences between the groups as due solely, or even mainly, to the differences in treatment. One factor, for example, that may have biased the results in favour of antihistaminic therapy was the increased attention given by the medical officer to the people receiving this. And though those on standard treatment had also an unusual amount of attention, this was not so great as in the antihistaminic group nor was any effect it may have had reinforced by the swallowing of tablets. But there can be no doubt that, in the circumstances of the present trial, people fared very much better with the new treatment than with the old, whatever factors may have been responsible for the difference.

If, however, the antihistaminic therapy is as advantageous as Tables 2 and 3 seem to indicate, then one would expect other evidence of this to have been revealed by the trial. This was so. The first important advantage was that while people had usually to be removed from contact with "tetryl" at an early stage of the standard treatment—for otherwise the dermatitis progressed—they could usually remain in full contact for the whole period of antihistaminic treatment, with consequent benefit to the worker in earnings and to production in output and costs. The second main advantage was the speed with which the new treatment controlled symptoms and signs.

Some of these differences are illustrated in Table 4, which summarizes the relevant data for the first 10 consecutive subjects in each treatment group of Table 3.

TABLE 4
FURTHER DIFFERENCES BETWEEN STANDARD AND ANTIHISTAMINIC TREATMENT

	Case No. in Each Group	Degree of Dermatitis†	Treatment Days to Clear		Total Treatment Days	Total Drug (mg.)	Average Daily Dose (mg.)
			Symptoms	Signs			
Standard Treatment :							
8 failures ..	1*	4	22	22		—	—
	2*	4	17	17		—	—
	4*	4·5	18	18		—	—
	5*	4	16	16		—	—
	6*	2	8	8	As	—	—
	7*	3	33	33	pre-	—	—
	9*	1	2	2	vious	—	—
	10*	2	26	26	column	—	—
2 successes	3	1	2	2		—	—
	8*	3	17	17		—	—
Chlorcyclizine Treatment :							
8 successes	1	2	2	7	7	700	100
	2	3	2	2	8·5	850	100
	3	4	1	12	12·5	1,250	100
	4	3	0·25	0·25	5·5	550	100
	5	1	1	1	6	600	100
	6	2	1	2	3	300	100
	7	4	2	4	6	600	100
	10	3	6	9	9	550	60
2 failures ..	8*	5	11	13	21	1,300	60
	9*	5	15	10	10	700	70

*Removed from contact for treatment.
†Assessed on following 5-point basis : (1) Erythema and itching ; (2) papular erythema, with or without itching ; (3) oedema or vesiculation ; (4) oedema plus vesiculation ; (5) marked oedema, vesiculation, and exudation. (People in stages 1 and 2 may leave work for "personal" reasons, but a keen worker would probably not report to the medical department until he was suffering from oedema and vesiculation (3).)

As will be seen from Table 3, there were two successes and eight failures in the standard group as against eight successes and two failures in the chlorcyclizine group. (It is possible that these first two failures with chlorcyclizine might have been avoided had larger doses of the drug been given, or had treatment been started earlier. Alternatively, these patients may not have taken all of the drug provided.)

Only one subject in the control group, a very mild case, was treated while still in heavy contact with "tetryl" as against eight in the chlorcyclizine group. As the proportions treated in and out of

contact respectively in these two sample groups are typical of the proportions in the standard and chlorcyclizine groups as a whole, they seem very definitely in favour of the antihistaminic treatment.

In the standard treatment group the average time required to clear signs and symptoms was about 16 days. In the chlorcyclizine group, however, symptoms were cleared in an average of about four days, and signs in about six, or, if the two failures are excluded, in under two days and five days respectively. These again are typical and noteworthy differences between the treatment groups and seem to afford still further evidence in favour of the antihistaminic treatment and, therefore, of some further investigation of it.

If antihistaminic treatment has such advantages over standard treatment as seem indicated by the evidence already given, then one would expect the new treatment to lower not only the losses to presswork of those who had to be removed because of dermatitis, but to lower also the number of those who chose to leave work of their own accord. That these expectations have been realized seems likely from a consideration of the data in Tables 1 and 5. In Table 1 the fate of 47 people who entered presswork, and for whom only standard treatment was available, was analysed. Table 5 shows in a similar way the position three months after the end of the trial period of the 48 people in all who had antihistaminic treatment for dermatitis.

TABLE 5
LABOUR TURNOVER OF PRESSWORKERS TREATED FOR DERMATITIS WITH AN ANTIHISTAMINIC DRUG

Total entering presswork and treated with antihistaminic		48
Number on presswork at end of period		25
Number lost to presswork by end of period		23
Reasons for Loss of Pressworkers		
Personal :	fear, discontent, staining of skin	8
Medical : 9	—Dermatitis	5
	—Other medical reasons	*4
Production :	moved to other jobs	6

*One of these died suddenly from coronary disease while still working in full contact.

By the time Table 5 was compiled, seven of the 20 people still on presswork at the end of the pilot trial period (Table 3) had been lost, three for medical reasons other than dermatitis and four for personal reasons. To the 13 remaining subjects from the trial period were added the 12 successes from the total of 17 subjects subsequently treated. Thus, looked at entirely from a production point of view, 25 pressworkers out of 48 were successfully maintained at work after chlorcyclizine treatment as against five out of 47 after standard treatment. But of the five people on presswork in Table 1, only two developed dermatitis and had the standard treatment : the other three were "immune". Thus, from the point of view of treatment in relation to production, the strictly comparable figures for those remaining in presswork in Tables 1 and 5 are two and 25 respectively.

The other main point evident from a comparison of these two tables is the lower loss for personal reasons in the group on antihistaminic treatment as compared with that on standard treatment, a drop of from 25 to eight. This may possibly have been because there was less fear of dermatitis, deriving from a growing appreciation by the workers of the safety, speed, and efficacy of the new treatment.

Even though caution must be exercised in drawing conclusions from these two seemingly comparable groups, the differences are sufficiently marked to be at least suggestive, and thus to favour some further investigation of chlorcyclizine therapy.

Conclusion

Without committing ourselves to the acceptance of any one of the several possible views concerning the mechanisms responsible for the skin reactions to "tetryl", or to whether the seemingly beneficial effects of the new treatment are to be accounted for by the chlorcyclizine, and, if so, to its antihistaminic action *per se* or not, all the results obtained seem to afford strong presumptive evidence in favour of the chlorcyclizine as against the standard treatment and constitute, therefore, a strong case for a rigorous controlled trial. For, if the impressions already given by the pilot trial could be confirmed in a rigorous trial, the considerations that would then apply to "tetryl" dermatitis might prove to be more generally applicable, and might lead the way to a better understanding of the nature and the possibility of control of some other forms of industrial dermatitis, and even have important repercussions in a wider field as well.

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The medical and labour problems presented by dermatitis in workers in heavy contact with "tetryl" are indicated.

As tolerance or "hardening" to the skin effects of "tetryl" commonly follows an attack of dermatitis, it looked as though a solution to both problems might be afforded by a safe treatment that either shortened the period of disability from dermatitis or enabled tolerance to be aquired without the

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development of marked signs or symptoms by men at work.

Since the primary manifestations of skin injury by "tetryl" are suggestive of histamine release, it seemed possible that antihistaminic drugs might serve these purposes. But before considering a rigorous trial to test this view it was necessary to find out from preliminary or pilot observations whether such a trial was likely to be worth while.

A pilot trial with the drug chlorcyclizine hydrochloride ("histantin") was accordingly undertaken.

While the conditions of the trial were far from ideal, the results show that chlorcyclizine is safe in the doses used even when administered to men at work, and that it seems to be highly effective and to offer marked advantages over the present standard treatment.

It is therefore concluded that the results give ample justification for a rigorous trial of antihistaminic therapy in the control of "tetryl" dermatitis.

Addendum

A rigorous trial was in fact started. Its design was similar to that of the Medical Research Council's large-scale trial of an antihistaminic drug in the common cold (Report of M.R.C. Committee, 1950) with the important difference that the drug was to be ingested in the presence of the medical officer and that the dose was to be varied if need be in accordance with the response of the patient. After 12 people had entered this trial, of whom only nine completed the treatment, it came to an abrupt stop. The successes of the pilot trial and subsequent period had led to a temporary solution of the labour problem, and as no further people were entering presswork no more subjects were available to us. (Of the nine people who completed this trial, six received the drug and three the inert tablets. Five in the drug group and one in the control group were subsequently continued in full contact.) The abortive nature of this trial is a further justification for presenting the results of the pilot investigation.

We wish to thank Mr. J. E. Jackson, O.B.E., Superintendent at a Royal Ordnance Factory, for the facilities he afforded us; Dr. N. Langdon Lloyd and Dr. A. D. K. Peters, O.B.E., of the Ministry of Supply, for their interest in the work; Dr. F. Prescott, of the Wellcome Research Institution, for supplies of chlorcyclizine; the Medical Research Council for an expenses grant to one of us, and the Ministry of Supply for permission to publish this paper.

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PERFORATION OF THE NASAL SEPTUM DUE TO SODA ASH

BY

R. McL. ARCHIBALD

From the Alkali Division of I.C.I. Ltd.

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Perforation of the nasal septum as a direct result of occupation has been recognized since the days of Rammazzini (Wampler, 1943). However, the unspectacular nature of the symptoms and its self-limiting nature have so conspired together to keep the condition from the public eye as to make references to it in the literature both few and cursory. Particularly is this true of perforation of the septum occurring amongst workers in soda ash.

Review of the Literature

St. Clair Thomson and Negus (1948) briefly mention perforation of the nasal septum due to syphilis and traumatic ulcers secondarily complicating rhinitis sicca. Marchand (1949) mentions the perforations of the septum which occur in cocaine addicts.

Perforations of the septum due to chrome and arsenical salts are frequently mentioned. Legge, (1934) writing of the effects of arsenic salts in the form of dust, says :

> " The most characteristic lesion . . . is perforation of the septum of the nose, resulting in a circular hole varying from one-eighth to one inch in diameter. Perforation may be complete in a month from the time of commencement of work. The anterior and lower margins of the cartilage and the bones to which they are attached never become involved in the ulcerative process, so that there is no deformity. . . . Once the perforation is complete, no further inconvenience is felt ; not a few workers are ignorant of the existence of the condition."

Collier (1940) claims that personal factors are more important than working conditions but admits the importance, as predisposing factors, of nasal deformity or obstruction. He quotes Prosser White (1934) as naming certain hygroscopic substances including lime, calcined spathic ores, cement, powdered sodium carbonate, tar and pitch, all of which may produce septal lesions. Collier is further of the opinion that ulceration and perforation occur below the level of the inferior turbinate where the stream of inspired air impinges on the septum. He is alone in suggesting that varied atmospheric humidity may lead to an increase in septal ulceration.

Müller is quoted by Ritchie Rodger (1934) as finding nasal perforations in more than 25% of 165 salt packers and sifters.

Ballenger, Ballenger, and Ballenger (1947) suggest that the convex side of a deviated septum is dried and irritated by the current of inspired air and its secretion dessicated leading to retrograde epithelial changes and ultimately to crusting and ulceration.

Marchand (1943) described in some detail his findings in calcium nitrate workers. In two factories the combined incidence of ulceration and perforations was 67% and 81%. He described in detail the break in the continuity of the mucous membrane, the ulcerations and crusting, the excavation, and finally the perforation. He mentions the symptomless nature of the occurrence. He thinks the lesions are due to the hygroscopic and caustic nature of the calcium nitrate.

Bernabei (1950) found no less than 10 perforations in 13 glass workers employed in mixing silicon dioxide with anhydrous sodium carbonate. The mixing process gives off a fine powder. It is postulated that sodium hydrate (NaOH) is formed and, being a strong caustic, produces lesions. Bernabei thought that the progress of the lesions could be halted by removal from contact with the dust. He asserts that there is a relationship between the size of perforation and the length of exposure but produces no facts to support these assertions.

Naidu and Rao (1948), in describing the manufacture of dichromates in India, state that ulceration of the nasal septum is seen in workers who concentrate and centrifugalize the dichromate solutions but make no mention of such lesions in the first stage of the process which involves mixing dry powdered chrome ($Fe_2Cr_2O_3$), lime

(CaO), and soda ash (Na_2CO_3). The resultant dust is said to cause upper respiratory lesions and is thought to be predominantly the lighter lime and soda ash.

Aupetit and Prévost (1951) found that four out of 10 men who worked with calcium cyanamide had lesions of the nasal septum, three perforations and one ulceration. However all the affected men were said to have worked a long time in the lime industry and it was to lime rather than to cyanamide that the lesions were attributed.

Where prophylaxis is mentioned by the above authors, dust suppression is given pride of place although the elimination of potential cases by selection at the pre-placement medical examination is tentatively suggested.

Soda Ash Manufacture : The Alkali Industry

It is only in the handling of soda ash that perforation of the nasal septum has been demonstrated so that this description will be confined to the terminal stages of manufacture and handling of this product.

Soda ash is manufactured from coke, limestone, and brine. It is a white powder, produced in chemically identical light, granular or dense forms, the microscopic appearances of which are illustrated in Fig. 1 (a–c).

The dried ash is mechanically packed into jute or paper bags. Dust is inevitably produced at the packing points despite exhaust ventilation. Soda ash causes rhinorrhoea and paroxysmal sneezing at first but the worker quickly becomes acclimatized. The taste can be detected in the mouth.

Packing soda ash, which is illustrated in Fig. 2, is a hot job and the packer does not like protective masks or mutton cloth. The temperature of the ash at the packing point varies from 120° to 130°F.

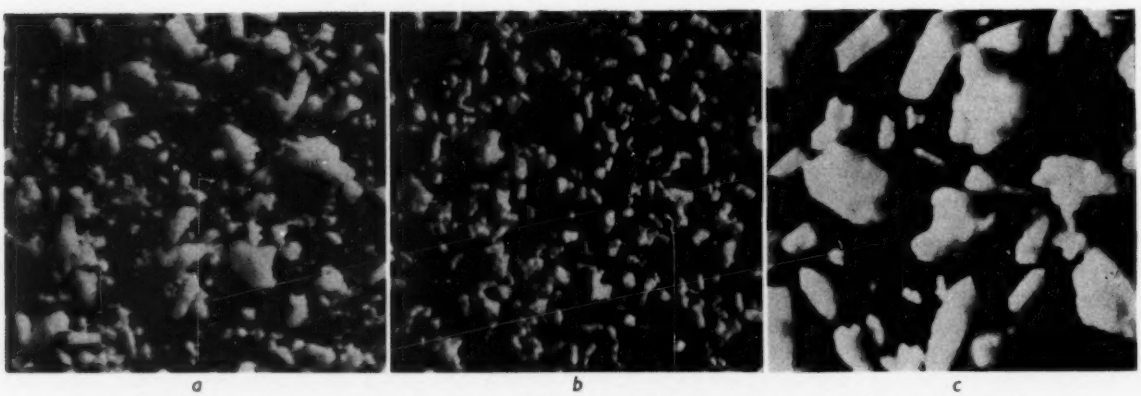
Considerable dust is also raised in the cleaning and repairing of returned jute bags. In busy periods up to 23,000 bags are handled daily in the bag plant. Bags caked with ash are mechanically beaten (Fig. 3). This is a very dusty operation performed exclusively by women who usually wear mutton cloth round their mouths and, sometimes, their noses. The volume of bags beaten is greater in wet weather when caking is more prevalent.

Bags which are not caked pass, together with those which have been beaten, to vacuum machines where residual dust is drawn from the interstices of the bag as illustrated in Fig. 4. Damaged bags are repaired by workers at sewing machines in the same room as the vacuums. There is generally a fine haze of dust over the whole room. Lastly there are checkers and "luggers" who stitch diagonally across the bottom corner of the bags to provide handholds.

Particle Size of Soda Ash Dust

Atmospheric samples of dust from a dense ash packing point in Factory A were examined by the combined thermal precipitator and settling tube methods. Counts showed that 66·14% by number and 0·22% by weight of the particles were less than 0·8μ in diameter and 95·80% by number and 4·19% by weight were less than 3·2μ in diameter. Much of this fine dust must be inhaled into the nose and an appreciable proportion will pass through into the respiratory passages.

Davies (1952) reviewing recent work suggests that 50% of particles with an effective diameter of between 3·5 and 5μ pass through the upper respiratory tract and that most of the particles larger than this are prevented by filtration from passing into the lungs.



a *b* *c*

FIG. 1.—The microscopic appearances of soda ash × 20. (*a*) Dense soda ash ; (*b*) light soda ash ; (*c*) granular soda ash.

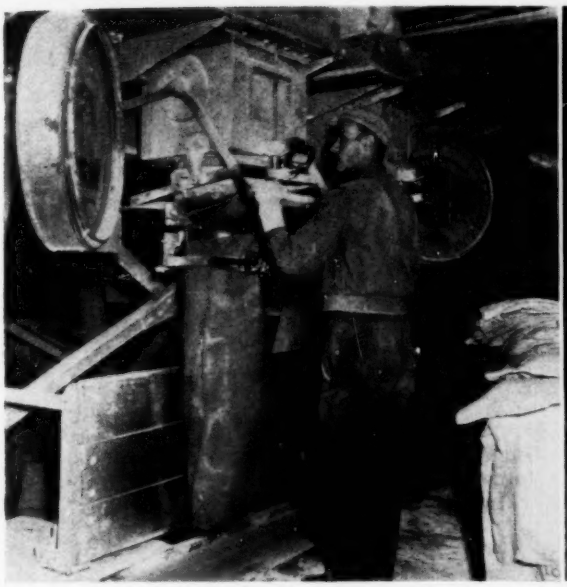


FIG. 2.—Packing of soda ash. The bag is secured to a spout. An automatic weighing machine is visible behind the packer on the right of the photograph.

FIG. 3.—"Beating" dirty bags. The bag is controlled by a pedal operated by the right foot. Note that this worker has mutton cloth round her neck but has not used it to cover her nose and throat.

Proetz (1941) points out

> "the human nose, in general lying more under the cranium than in front of it, shows a greater tendency to depart from the normal. This tendency often exhibits itself in the form of a deflected septum. . . . The effect of restricting, deflecting, or otherwise concentrating air streams, particularly during inspiration, upon any localized area of the mucosa may be very serious. Inspired air playing in a jet upon a restricted area rapidly evaporates the mucus, increasing its viscosity and preventing its movement by the cilia."

In writing of the effect of dust particles on the normal nose he avers: "The dusts react only through some specific physical or chemical property peculiar to them, for inert dusts, even in large amounts, are carried off without any disturbance of the membrane".

Scope of Present Investigations

Reference has already been made to the types of work which involve exposure to soda ash dust. Three groups of work people were examined at factories A and B as follows:

Group 1.—This consisted of ash packers, bag-stitchers, and checkers of weight at factories A and B. These workers weigh and pack the ash from spouts into jute bags as illustrated in Fig.2, the bags being then stitched with twine by a manually operated machine. The men are constantly exposed

FIG. 4.—Cleaning bags by vacuum. The worker is about to operate the vacuum with his right foot. This will draw the bag up to the spout and in anticipation of this he has shut his eyes to avoid the puff of dust which arises with each operation.

to a heavy concentration of ash dust. They number 63, are all males, and are mostly shift-workers.

Group 2.—This group consisted of bag plant workers, all of whom are employed at Factory A. There are two shift teams, the majority of whose members rotate on specific jobs, namely, lugging, darning, vacuum-cleaning and beating dirty bags. The day workers are employed on a variety of jobs which involve the handling of both clean and dirty bags within the precincts of the plant. All workers are contaminated to some extent by soda ash dust although the degree of contamination varies. There are 156 employees in this plant, 91 men and 65 women.

Group 3.—Group 3 included workers of both factories, 100 consecutive patients who consulted the doctor at each works surgery for any reason being examined. Work people who are already included in the survey in Groups 1 or 2 were excluded. The remainder formed this control group. The exposure to soda ash might vary from slight to heavy and might be intermittent or constant.

The people employed in any one plant are continually changing for a variety of reasons, and in order to ensure constancy of the clinical material the members of Groups 1 and 2 consist of those actually employed in the work described on January 1, 1952. Whatever happened to them after that date they were still included in these groups. The collection of the controls in Group 3 was begun on the same date at both works. Where a patient's age is quoted it refers to age on January 1, 1952.

Group 4.—Group 4 was studied as a further control and consisted of 100 male applicants for employment. By reference to their previous occupations, as stated on the Ministry of Labour Form ED. 10, it was ascertained that 99 had not been employed in industries or manufactures in which soda ash is regularly used in more than small quantities. One man had a brief previous period of employment at Factory A.

Broadly speaking, therefore, the four groups resolved themselves as follows : Group 1, continuous exposure to soda ash dust ; Group 2, fairly continuous exposure to soda ash dust ; Group 3, intermittent, occasional, or slight exposure to soda ash dust ; Group 4, no exposure to soda ash dust.

Method of Examination

A caliper, which could be inserted into the nose between the blades of a nasal speculum and by which the size of the aperture could be measured, was made by the instrument department (Fig. 5).

FIG. 5.—Caliper for measuring the diameter of perforation of the nasal septum.

Attempts have been made to photograph some perforated septa and the following technique was finally used. The patient lay on a trolley with the head steadied by sandbags to prevent movement. The light from an ophthalmoscope, from which the lens system had been removed, was inserted into the left nostril and directed towards the septum. The room was completely blacked out and the camera pointed into the right nostril, the ala of which was held back by one blade of a nasal speculum. The photograph was taken at an exposure of 10 seconds at *f*/ 11 on Una quarter plate.

Clinical Findings

The details of the age groups and length of exposure to soda ash (Groups 1 and 2) or length of service (Group 3) are shown in Table 1.

TABLE 1
AGE GROUPS AND LENGTH OF EXPOSURE AND SERVICE

Age (years)	Nos. Examined					Average Exposure to Soda Ash (yrs. mths.)			Average Length of Service (yrs. mths.)
	Groups					Groups			Groups
	1	2		3	4	1	2		3
		M.	F.				M.	F.	
Up to 19				14					2 6
20–29	15	28	9	31	43	2 0	7 10	3 5	3 2
30–39	17	33	19	41	44	6 0	6 3	5 10	7 3
40–49	15	14	30	49	13	15 0	16 7	7 5	17 5
50–59	11	13	7	41	0	15 7	27 7	10 4	28 10
60+	5	3	0	24	0	32 5	47 0		35 3
Total	63	91	65	200	100				

Group 1.—Among 63 of the men, five cases of perforation of the nasal septum were found and two cases in which thinning of the septum was so marked on both direct inspection and transillumination that they were judged to be cases of impending perforation.

Five of these seven cases were in the 40–49 age group and had exposures ranging from 15 months to 20 years on this type of work. The youngest patient, one with impending perforation, was 26 years old and had had only nine months' exposure.

The perforations are circular or oval and the margin appears to be totally covered by mucous membrane which presumably dips in from either

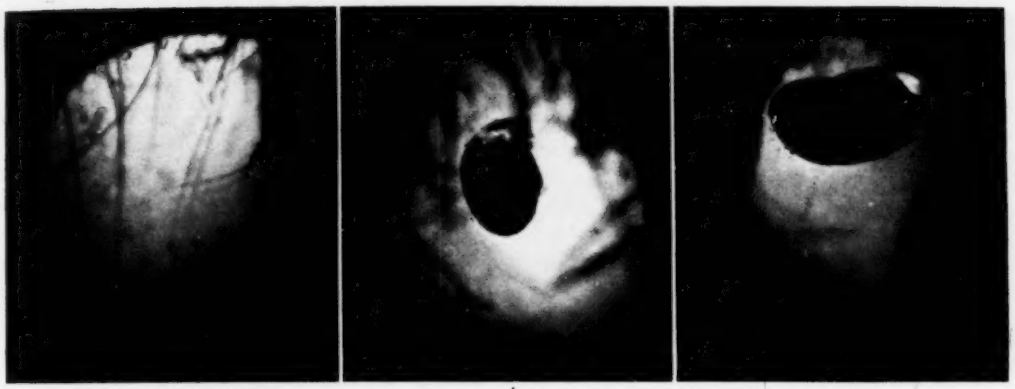


FIG. 6.—(*a*) Normal septum. (*b*) Perforation of the septum. The perforation is approximately 0·7 cm. in diameter. (*c*) Perforation of the septum. The perforation is 1·3 cm. in its greatest diameter.

side as the lesion develops and ultimately becomes continuous. All the perforations are sited anteriorly in the cartilaginous portion of the septum. A normal septum and two perforated septa are shown in Fig. 6. The greatest diameter varies from a few millimetres to centimetres.

The appearance of an ulcerated septum is as follows. There is loss of mucous membrane, shallow, sloping edges leading down to the hollowed area which is often covered by a crust of caked ash or inspissated mucus. Careful removal of the crust reveals the raw ulcerated surface. Ulceration may be found on either the convex or concave side of a deviated septum.

Without exception, no workman examined was aware of or complained of any abnormality in the nose. Even large perforations appear to be entirely symptomless.

There were also five cases in which atrophy of the septal mucosa was obvious to the naked eye. The appearance of the atrophic mucosa is characteristic. The septum is gently cleaned with a moistened swab after which the mucosa appears pearly grey to dull off-white with no sharply defined margin, shading rather into the normal mucosa.

There were thus in this group 12 cases (19%) with abnormal findings which might fairly be attributed to the effects of soda ash.

Group 2.—In this group of 156 workers there were 14 perforations of the septum, five impending perforations, and 10 cases in which there was some degree of atrophy of the nasal mucosa. This makes a total of 29 cases (18·6%) with abnormal findings which could be attributed to the effects of soda ash. Perforations were seen more frequently in women, there being 11 (17%) as opposed to three in male workers (3·3%). On the other hand, abnormal appearances of the nasal mucosa were commoner in men (nine cases, 10%) than in women (one case, 1·5%). Altogether 24·6% of the women and 14·2% of the men showed some abnormality.

Group 3.—In this group of 200 employees only two perforations were found but there were some 11 cases in which atrophy of the nasal mucosa or thinning of the septum could be demonstrated, that is 13 cases (6·5%) with abnormal findings. The perforations were found in a shift-worker with over 50 years' service and a labourer with barely two years' service. The abnormalities noted were similar to those found in the previous group. The ages of the two subjects with perforation of the septum were 64 and 42 respectively.

Group 4.—The previous occupations of the 100 consecutive applicants for employment were very various and many had changed their occupations so frequently in the last 10 years as to render invalid any conclusion which might have been tentatively drawn. The average age of the group was 31 years 6 months. No significant abnormalities were found in this group. It is realized that the age groups are not strictly comparable to those of Groups 1 – 3, but it is felt that this does not materially affect the validity of this control group.

One man in this group had had 15 months' previous service at one of the factories, otherwise none had been previously employed in alkali manufacture.

No reference has been made to other abnormalities which were found, such as deviation of the septum with or without spurs, hypertrophy of one or more

turbinates, and polypi. It became obvious that the appearance of the nose gave little indication of what one might expect to find on further examination. Lesions were found in narrow and broad noses, in symmetrical noses with straight septa and in noses with gross deviations, in noses where chronic hypertrophy was marked, and in others where there was no evidence of inflammation or infection. As it is not the intention of this paper to study the incidence of such abnormalities they have not been considered in the final conclusions.

Discussion

Although the numbers are not large these results show that there is a definite occupational factor in the production of perforations of the nasal septum.

No figures of the general incidence of perforation of the nasal septum in the general population are available but J. A. Kilpatrick (personal communication) states that in his experience it is considerably less than 1%.

Two broad lines of approach to the problem of causation become apparent. First, it might be suggested that the longer an employee works with soda ash the more likely is he to show signs of septal damage. Accordingly Groups 1 and 2 were analysed by length of exposure to soda ash (Table 2). The average exposure of each age group was also computed (Table 3). The number of lesions found in each group are also shown.

TABLE 2
SEPTAL DAMAGE RELATED TO LENGTH OF EXPOSURE TO SODA ASH

Duration of Exposure (years)	Group 1	Group 2		Total	Percentage Affected
		M.	F.		
Under 1	1/6	0/2	0/4	1/12	8·3
1–3	1/15	0/20	4/21	5/56	9·0
4–7	1/10	3/22	2/8	6/40	15·0
8–9	1/6	0/5	2/10	3/21	14·3
10–19	2/14	1/21	7/22	10/57	17·5
20–29	1/7	0/8	0/0	1/15	6·7
30+	0/5	0/13	0/0	0/18	—
Total	7/63	4/91	15/65	26/219	11·9

TABLE 3
SEPTAL DAMAGE RELATED TO AGE

Age Groups (years)	Group 1	Group 2		Average Exposure for All Groups	Percentage Affected
		M.	F.		
20–29	1/2y. 1m.	0/7y. 10m.	1/3y. 5m.	2/5y. 5m.	4·0
30–39	1/6y. 1m.	2/6y. 3m.	4/5y. 10m.	7/5y. 1m.	10·1
40–49	5/15y. 1m.	1/16y. 7m.	8/7y. 5m.	14/11y. 7m.	23·7
50–59	0/15y. 9m.	1/27y. 7m.	2/10y. 4m.	3/19y. 6m.	9·9
60+	0/32y. 7m.	0/47y. 0m.	–	0/38y. 0m.	—

The numbers are too small to show any statistical significance. Nevertheless the incidence of perforations and near perforations rises with increasing length of exposure up to 20 years. For longer exposures the incidence falls for which no explanation can be offered.

If the workers in Groups 1 and 2 are split into under-40 and over-40 years of age it is found that the incidence of perforations and impending perforations in the former group is 7·4% and in the latter 17·3%. In spite of the longer exposures of the older men, these figures suggest a greater incidence in the older workers but give no indication of the age of onset of the lesion.

It is also noteworthy that the incidence of perforation and impending perforations in women in Group 2 is 16·9% as compared to 3·3% for men in the same group. The main difference between the two groups is that the dustiest job of all, namely beating returned bags, is done entirely by women and the next dustiest job, namely the vacuum-cleaning of returned bags, is done largely by women. Lugging, done solely by men, is not a dusty occupation. Possibly this difference in the type of work done is related to the higher incidence of lesions in women.

The second possible approach is that there is some factor in the structure or function of the nose which predisposes to perforation. This would not seem to be borne out by the above findings. It might be suggested that lesions would start on the convex side of a deviated septum. But examination of cases of perforation in which a deviation coexists gives no clue as to which side was first affected. Similarly mucosal atrophy and thinning have been observed on both convex and concave sides of deviated septa.

In the light of our own experience it is thought that the stream of inspired air containing fine particles of sodium carbonate does in fact impinge on the

septum. A solution of continuity presumably occurs followed by ulceration and perforation as already described. Cases can be demonstrated, however, in which the septal mucosa is grey and lustreless and it is thought that this appearance may precede ulceration.

Examination of our cases does not enable us to say whether the initial lesion arises on the concave or convex side of a deviated septum, as once the perforation is complete there is nothing to indicate which side was first affected. Ulceration has been found on both convex and concave sides.

The presence of deformities of the septum is no indication that ulceration will take place as many workers with deviated septa show no pathological changes.

The perforations do not appear to enlarge once the margins have become covered with mucous membrane. This is presumably because no further dust impinges on the septum and also because of alteration in the flow of inspired air which enables the dust to disperse more widely within the normal cavity.

Conclusion

When a symptomless condition such as this is discovered there must always be the temptation to " let sleeping dogs lie " and do no more about it. On the other hand, the septum has a physiological and anatomical role to play and alteration or modification of its structure must be potentially, if not actually, harmful.

With this in mind, it is obvious that the main approach must be to reduce the dust, and if possible, eliminate it. A nasal examination of all applicants for employment and subsequent periodical examinations in our own works would probably lead to an undesirable focusing of attention on the nose and a consequent possible production of neurosis. To exclude from employment those with nasal abnormalities would be equally impracticable even if we were quite sure what types of abnormal nasal structure or function predispose to perforation.

A parallel could be drawn with the far graver problems of pneumonoconiosis where the solution lies not in the hands of the doctor so much as in those of the engineer.

Summary

Perforation of the nasal septum has received little mention in medical literature.

The scope of the present investigation is defined and two groups of workers, namely ash packers and bag plant workers, and two control groups, one chosen from the two works and one from applicants for employment, are analysed. These groups are exposed respectively to large, moderate, slight, and negligible quantities of soda ash dust.

The incidence of perforations and impending perforations in four groups with large, moderate, slight, and no exposure to soda ash dust was respectively 11·1, 12·1, 1, and 0%. In addition, abnormalities of the septal mucosa which might be attributed to the effects of soda ash were seen in 8·0, 6·4, 5·5, and 0% respectively.

A caliper to measure the diameter of the perforations is described.

My thanks are due to members of the Research Department of the Alkali Division of Imperial Chemical Industries Limited for information on particle size and for advice on statistical matters, and to Mr. W. J. Jackson who took the photographs. Also to Dr. D. A. K. Cassells and Mr. J. A. Kilpatrick for their constant encouragement and advice.

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THE EFFECT OF THE DRINKING PATTERN ON WATER ECONOMY IN HOT, HUMID ENVIRONMENTS

BY

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Work in a hot, humid environment, whether in some unfavourable industrial situation in the temperate zone or in a tropical climate, involves the worker in a high rate of water loss by sweating. Since any marked degree of water debt is undesirable, if only from the subjective aspect, provision must be made for water replacement.

A man's drinking pattern is conditioned by two main factors, the thirst mechanism and the availability of water. The thirst mechanism is notoriously inadequate since it has been demonstrated (Adolph, 1947) that even when exposed to an unlimited supply of water a man may contract a water debt amounting to about three-quarters of a litre, the phenomenon of " voluntary dehydration ". When the water supply is limited the problem is complicated by the fact that the most economical use must be made of the available supply. If large volumes of water are drunk at any one time a water diuresis will result and the excess water excreted through the kidney is thereby lost to the more desirable route of evaporation through the skin by which heat may also be dissipated.

The experiments described in this paper were made to determine the most economical way physiologically of administering a water ration to a group of men exercising in an environment representative of the climatic conditions found in a deep mine in Nigeria (Ladell, 1951).

The six subjects were typical members of the Lagos labour force who had been trained to empty the bladder completely at frequent intervals without recourse to catheterization. They exercised in a climatic chamber maintained at a temperature of 100° F. dry bulb, 93·5° F. wet bulb, by stepping on and off a stool 12 inches high 20 times per minute for five minutes in each quarter of an hour. The air movement in the chamber was turbulent and at a rate of less than 50 feet per minute. One experiment was performed at each drinking pattern and the exposures were spaced at least one week apart in order to avoid the risk of the subjects becoming acclimatized to the experimental conditions.

In each experiment the total exposure consisted of six cycles of work and rest, 90 minutes in all. The men were weighed at the start of the experiment immediately after emptying the bladder, and at the end of each of the six cycles the following measurements were made: (1) The men were dried with a towel to remove unevaporated sweat and then weighed. (2) The men emptied their bladders and the volume of urine excreted was measured. (3) Rectal temperatures were taken.

During a preliminary experiment it was found that when no water was drunk the men, at the end of the experiment, were approximately 1 kg. lighter than at the start of the exposure, i.e., they had contracted a water debt of about 1 litre, since under these circumstances almost the entire weight loss was due to urinary or cutaneous excretion of water.

It was decided, therefore, to adopt a volume of 1 litre of water as the fluid ration for this exposure and to administer this volume in various ways in order to decide which fashion of administration was the most economical. The desirable pattern is presumably the one which provokes the least diuresis and enables the man to finish his spell of work at the same body weight as that at which he began.

The patterns of water administration were (*a*) 1,000 ml. at the start of the experiment, (*b*) 333 ml. at the start of the experiment and two further doses of 333 ml. at intervals of 30 minutes, (*c*) 167 ml. at the start of the exposure and every subsequent

TABLE

WATER BALANCE STUDIES FOR 90 MINUTES OF MEN WORKING (STEP-CLIMBING) IN A HOT, HUMID ENVIRONMENT

Experiment	Drinking Pattern	Water Debt (ml.)	Water Turn-over (ml.)	Urine Loss (ml.)	Non-urinary Loss (ml.)	Change in Rectal Temperature (°F.)
Control	None	1,026 ± 153	1,026 ± 153	81 ± 17	945 ± 174	3·66 ± 0·60
a	1 dose of 1,000 ml.	446 ± 218	1,446 ± 218	371 ± 207	1,075 ± 74	3·18 ± 0·37
b	3 ,, ,, 333 ml.	369 ± 123	1,369 ± 123	227 ± 82	1,142 ± 112	3·20 ± 0·22
c	6 ,, ,, 167 ml.	215 ± 111	1,215 ± 111	170 ± 49	1,045 ± 60	3·10 ± 0·60
d	12 ,, ,, 83 ml.	100 ± 109	1,100 ± 109	82 ± 29	1,018 ± 88	2·90 ± 0·30

15 minutes, (*d*) 83 ml. at the start of the exposure and every subsequent seven and a half minutes.

Results

In the Table are recorded mean values and standard deviations for the following functions: (1) Water debt, i.e., the difference between the initial and final weights expressed in terms of millilitres of water; (2) the water turn-over, the water debt plus the volume of water taken during the experiment; (3) the volume of water excreted in the urine; (4) the non-urinary loss of water, calculated from the water turn-over minus the urinary loss; (5) the change in rectal temperature during the exposure.

It will be observed that in the case of all drinking patterns except (*d*) the volume of urine excreted is greater than that excreted during the control experiments when no water was taken. Statistical analysis of these values reveals significant differences at the level of $P<0{\cdot}01$. There is also a significant difference between the water debt values obtained in the control experiments and in patterns (*a*), (*b*), and (*c*). There is no significant difference between the values for non-urinary water loss in the various experiments.

Discussion

These results indicate that when water is taken in volumes greater than about 100 ml. at one dose a significant diuresis results leading to a greater loss of body water during the experimental exposure. If a man, therefore, is to use a water ration to the greatest advantage he must drink small volumes frequently rather than larger volumes at longer intervals.

The fact that a man takes his water ration in frequent small doses leads to a saving of between 300 and 400 ml. of water during the 90-minute period. The saving over a whole eight-hour shift spent at these temperatures will be considerable and in circumstances where the water supply is limited may make the difference between the man's being able or not to finish his shift.

It is probably impossible to achieve the ideal condition of very frequent drinking in the average industrial situation as the process is tedious but these results emphasize the need for a freely available supply of water in hot industrial situations and for the education of the worker in the habit of more frequently drinking smaller volumes.

Summary

Experiments on the male West African exercising in a hot, humid environment similar to that found in the mines of this area have demonstrated that a considerable saving in water required by the subjects can be effected if small volumes are taken at frequent intervals rather than large volumes taken less frequently. This finding may be of considerable importance in situations where the water supply is limited.

The author is indebted to Dr. D. W. Horn, Statistician to the Department of Medical Services, Nigeria, for the statistical examination of the results.

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THE MILL REEK AND THE DEVONSHIRE COLIC

BY

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According to the Statistical Account of Scotland (Maconochie, 1792) the village of Leadhills in Lanarkshire contains the most famous and ancient lead mines in Scotland. They were included in a grant of lands to the monks of Newbattle Abbey in 1239 and, from a lawsuit soon afterwards, it is clear that the mines were in production about that date. Depending on demand and the price of lead they have been worked periodically ever since. They are at present closed but re-opening is again in progress.

Tennant recorded (Porteous, 1876) in 1772 that :

> " the veins vary in their depth. Some have been found filled with ore two fathoms of the surface ; others sink to the depth of ninety fathoms. The varieties are the common plated ore (galena) called potter's [this may refer to the use of lead in the glazing of earthenware vessels], the small or steel grained ore, and the curious white ores, lamellated and fibrous. The working of this species is much more pernicious to the health of workmen than the common."

The veins of lead, sometimes bounded by a girdle of quartz, popularly called " riders ", occur generally in greywacke or greywacke slate, very hard, highly siliceous rocks. It may be of interest to record here in passing that gold is also found in the neighbourhood. These facts, associated with frequent references to the prevalence locally of chest disease including fibroid phthisis, suggest that the miners suffered from silicosis though the disease was usually attributed to the wet, inclement climate.

Here is an early picture of the smelting works.

> " At the furnace were men enduring the blaze of the red heat. They were piling up the glowing coals upon the bruised and washed ore in the receptacle in the furnace : and from under the front of the fire we saw the molten lead running down its little channel into its own reservoir, leaving behind the less heavy dross, which was afterwards to be cast out in a heap in the yard."

In 1792 the mines were worked by the Scotch Mining Company who employed 200 men. These comprised pickmen, smelters, washers and labourers, besides carpenters and smiths. Pickmen and smelters earned eighteen to twenty pounds a year, while the washers, who were very young, received less. The overseers purchased meal and barley of which it is recorded that " all the hands employed receive every week a certain quantity for their families, which makes part of their pay ".

The men worked only five or six hours in the twenty-four and for five days in the week. This no doubt reflects the adverse conditions underground and around the smelter. As a result the men had a great deal of spare time which they employed in reading. For this purpose they fitted up a library out of which everyone who contributed received books. This benefit has been ascribed to Allan Ramsay, the Scots poet, who was born at Leadhills in 1686. Moreover, in this we note the early beginnings of mechanics' libraries and, later, mechanics' institutes during the Industrial Revolution. These developments were, in turn, the inspiration of adult education, a movement which began in Scotland and spread through industrial England (Trevelyan, 1946). One of the great pioneers was Dr. George Birkbeck of the Andersonian University of Glasgow (Oakley, 1946), whose name is still memorialized in the college which he founded in London. As to the quality of the reading and the readers the Rev. J. Moir Porteous, in writing of shepherds, records that : " Lectures have been delivered on these hills by a shepherd which would have done no discredit to an LL.D. or D.D. " Lest we appear to protest our virtues it may be added that " yet a rougher party can rarely be met with than that of some young shepherds when ' whuskied ' at a village fair. Then the drink madness shows the dark beginnings of the darker end ".

The prevailing distempers or ailments among the local population were rheumatism and the scurvy. The latter was attributed to the use of salted mutton and beef, of which the people were extremely fond, while at the same time being averse to vegetables.

The humidity of the air was blamed for the rheumatism but it may not have been unrelated to employment at the mines or, indeed, to contamination of the air and water by lead.

In the course of a tour through Great Britain the Rev. C. Cruttwell recorded in 1801 that :

> " The appearance of Leadhills is disagreeable in the extreme ; rocky, rude and barren, every vegetable is raised with difficulty, and seldom brought to perfection. Spring water is to be obtained of excellent quality, but that which is below the smelting mills is poisonous. The lead ore, before smelting, is broke very small and washed from filth, which frequently contains arsenic. Fowls of any kind do not live many days at Leadhills ; horses, cows, dogs, and cats often find ill effects of this poisonous mineral."

It was estimated that one-tenth of the lead passed away with the smoke. In due course brick and woodwork chambers were erected to precipitate the fumes in flues by a system of water sprays. When these chambers were first cleaned out after working seven months, 58 tons of lead, valued at £1,300 sterling, were recovered.

The effect on livestock and vegetation in the village and surrounding hills is described thus :

> " Mossy land, where, as at the edge of rocks, the grass has not a firm hold of the soil, but which springs up quickly and is eagerly sought after by the sheep, is found to be injurious, much soil being swallowed. So also is the smoke of the lead furnaces, which is seen in the morning lying as dew upon the heather or grass."
>
> " Dogs and cats are shortlived. They take the ' lead-brash,' wheel round and die."

These observations, as will appear later, are common to all lead-mining areas. Popularly the ailment is known as bellan or the belland, which, according to the English Dialect Dictionary means " a kind of colic, in man or animals, caused by swallowing particles of lead ore ". The references, however, to fits and weakness may signify the occurrence of nervous disorders.

Old workers still resident in the now semi-deserted village recall that following a successful action in the early 1900s by a local farmer against the mining company, in respect of injury to his lands and cattle, smelting at the Leadhills mine was discontinued. In recent years we have had similar experiences in relation to fluorine fumes from aluminium works and steel foundries and the London " smog ". It is incongruous that the well-being of the community must await the malign influence of atmospheric and water pollution on pedigree cattle. The following article which appeared in the *Scots Magazine* in June, 1754, seems worthy of reproduction in full. It is called " An Account of the Disease called Mill-Reek ", and it was written by Mr. J. Wilson, surgeon at Durrisdeer.

" All the inhabitants at Leadhills are subject to this disease ; but it mostly seizes, and violently affects the men whose daily business it is to melt down the lead. The reek or smoak rising from the melting is believed to be the cause of the disease ; because the melters, who are most subject to it, are most exposed to the smoak, which comes out often full in their faces. The melting houses are called *mills*, because the bellows are worked by water-mills.

In the slighter stage of this disease, an uneasiness and weight is found about the stomach, especially near the cartilago ensiformis ; and sometimes it appears like a colic in the intestines. The spittle of the sick is sweet, and something of a bluish colour, resembling what one observes when he chews lead. The pulse is a little low ; the skin is all over cold ; and a clammy sweat frequently breaks out. The legs become feeble, with a prickling numbness ; and there is a debility and laziness in all the body. The appetite goes away, and they do not digest what food they take. Sometimes a *diarrhoea* makes a cure ; but if it continues too long, it is very hurtful. In this *stadium* the sick are yet able to go about, and to work.

But if these symptoms continue long, and spirituous liquors are drank with an empty stomach, or after working lead, the disease comes to its second stage ; in which to the former complaints are added a fixed pain in the stomach and guts, especially in the lower part of the abdomen, extending itself from the one *os ilium* to the other. The patients become very costive, with the sense of somewhat gnawing their intestines ; and the pulse turns quick, with heat on the skin. Giddiness, with vehement pain, seizes the head ; which is succeeded by an insensibility and delirium, like madness of the worst kind ; insomuch that they tear their own flesh, and bite their hands ; the extremities tremble and are convulsed ; at last they fall low, the pulse intermits at every third or fourth stroke, and they die in a *coma* or apoplexy.

If proper medicines are given in the first stages of this disease, the patient generally recovers ; if it goes on till giddiness begins, the success is doubtful ; and when the cure is delayed to be attempted a little longer, the disease almost constantly proves mortal.

If the work-people at Leadhills would use the following precautions, they might save themselves from this disease, at least would have it very mild.

1. No man ought to go to work fasting ; and he ought to take oily or fat food. A glass of sweet oil pure, or mixed with a little *aqua vitae*, would be a good morning-draught.

2. Physic should be taken spring and harvest, and whenever any effects of the reek are felt.

3. Ardent spirits ought to be drank very sparingly ; and never in time of work at the mill, or immediately after it.

4. No mill-man, when heated by work, ought to go into cold air, but to put on his cloaths immediately, and return to his lodging, to change his working-cloaths for others, and cool gradually.

5. Immediately after coming from work, the aliment should be mostly liquid, as broths.

6. Low and poor diet makes them more liable to be affected, and less able to undergo a cure.

7. When their business can allow, they should go out of the reach of the reek, to breathe an untainted air, and to take victuals free from lead. But I must caution the labourers at Leadhills, not to take long journeys; they are more hurt by travelling one day, than by working two.

The cure of this disease depends principally on cleansing the *primae viae*; and therefore after blooding such patients, if they are plethoric, I give them a vomit of *emetic wine* or *tartar*; which must be a dose double to what would vomit another person. Half a dram of *vitrum antimonium* is a dose; and during its operation, warm water is to be drank plentifully. If the vomit operates well, and purges briskly too, the patient is in a fair way of recovering; which a second, but a milder dose of *ipecacuana* with some *tartar emetic* mixed, often makes compleat; but if the emetic neither vomits nor purges, the patient is generally worse for it; and a stronger dose should be given soon. If it vomits, but does not purge, a cathartic of the antimonial kind, or of jalap and mercury, in greater than ordinary quantities, ought to be given: and during the time of purging by the emetic or cathartic medicine, the patient ought to drink warm broth plentifully. The vomits and purgatives ought to be repeated at proper intervals, till the uneasiness in the stomach and guts is gone. If these medicines overdo, an opiate may be given at night. But this is to be administered sparingly, lest it bring or increase costiveness, which is the worst thing can befal the patient. At the same time, emollient, anodyne, and laxative clysters, are frequently to be injected, for emptying the guts, if the purgatives do not their duty.

When blood or matter are passed with the *faeces*, the emetics and purgatives are to be abstained from, till, by healing balsamic, but laxative clysters, and mild food, this appearance ceases.

When the belly is much swelled, emollient fomentations, should be often applied to it; but if the madness is begun, little else can be done, than to endeavour to keep the patient quiet, during the little time he has to live.

Sometimes it happens, that after the complaints of stomach and guts are gone, a prickling pain and feebleness remain in the leg, much like to a rheumatism. For which, friction, with a coarse cloth or flesh brush, is necessary. If that fails, *ung. nervinum*, with *ol. terebinth.* mixed, is to be rubbed on every night, before the fire: after which the member is to be wrapped in flannel. If these pains are violent, or the feebleness resembles a palsy; blisters ought to be applied to the skin under which the large nerves are situated, and the medicines proper in a palsy are to be given.

Some are so wasted before the cure is completed, that they remain afterwards emaciated, weak, and as if they were hectic, with a giddiness in their head: and sometimes they chat to no purpose, or seem hypochondriac. In this condition, the patient should go to the country, to ride a horse-back some miles every day; and at the same time should take bitters, with bark and steel. If the giddiness continues, I have given, with success, *pilul. de myrrh* with a small proportion of *camphor*."

Earthen Wares Glazed with Lead

In May, 1953, under the auspices of the Nutrition Society, a gathering of distinguished scientists met in Edinburgh to mark the bicentenary of the publication of Lind's *Treatise on Scurvy*. His *Essay on the most Effectual Means of Preserving the Health of Seamen in the Royal Navy* is unfortunately less well known. Intervening between these two publications he contributed a short article to the *Scots Magazine* of 1754. It appeared in the May issue, that is one month before Dr. Wilson's article. His purpose was to comment on lead poisoning and, as will appear, the matter was not unrelated to the prevention and treatment of scurvy by the use of fresh fruit juices. He writes

> "I received the following information from a gentleman in London:
>
> 'That, intending to make the extracts of lemons, he squeezed the juice of a thousand lemons into a large glazed coarse earthen vessel, and allowed it to stand for two days: he then poured off an English gallon of the clear juice into another glazed flat earthen vessel, and put it in a pot of boiling water to evaporate. During the evaporation, a great quantity of sediment appeared among it, which, upon examination, he found to be the salt or sugar of lead, to the quantity of several ounces. He then poured off the remaining part of the juice of the first earthen vessel, which had not been put upon the fire, and was surprised to find the sides and bottom of it also loaded with a large proportion of the same sort of salt.'"

Lind attributed the effect to solution of the lead glaze of the vessel by the acids in the juice, a fact previously observed in relation to vinegar, cyder, and Rhenish and Moselle wines, and classically as the colic of Poitou. He argued that such earthenware vessels were unsuited to the purpose and advised that

> "the most proper vessels for preparing the inspissated juice of lemons, oranges or any other acid fruits, are, first, porcelane, or china ware. The substance of these is of so close a texture, that no saline or other liquor can penetrate them. The glazing, which is made likewise of the substance of the china is so firm and close, that no salt or saline substance can have the least effect upon it."

He also considered as equally suitable the stone ware commonly called Staffordshire.

Thirteen years later on the 29th day of June, 1767, before the College of Physicians in London, Dr. George Baker (later Sir George Baker, Bart.) read *An Essay concerning the Cause of the Endemical Colic of Devonshire*, the earliest account of which had been published in 1703 under the title *Dissertatio de Arthritide Symptomatica* by Dr. William Musgrave. Baker in his review of the subject referred particularly to Dr. Huxham's *Opusculum de Morbo Colico Damnoniorum* published in 1739, in which it is recorded that :

> " In the beginning of the Autumn 1724 it (the colic) spread itself over all the county of Devon, among the populace especially, and those who were not very elegant and careful in their diet ; and that, though it may not rage with the same degree of violence, and may affect a vastly less number of people, yet it infests that county more or less every Autumn."

Dr. Huxham was of opinion that the cause of the Devonshire colic was " a very gross, essential acid salt, or tartar, with which the expressed juice of apples, whilst unfermented, abounds ". His explanation of the symptoms is of no little interest.

> " By long and frequent drinking a liquor of this kind, such a quantity of crude, gross tartar is thrown into the blood, that it thence becomes very acrid ; and not only the blood, but, from that impure source, all the humours thence secreted. So that instead of a very soft, lubricating mucus separated by the glands, discovered by Dr. Havers, we have as it were a sharp, coagulated matter, whence arises a great pain in the joints, and impotence of their motion. Instead of an exceeding soft lymph to moisten the nerves, a corrosive ichor ; and hence epileptical attacks."

Baker dissented from these views and asserted that the colic was precisely the same disease, which is the specific effect of all saturnine preparations. He suspected that the disease was not in pure cyder but in some, either fraudulent or accidental, adulteration.

As an index of the incidence of the condition, Baker cites Dr. Andrew of Exexter who gives the following numbers of patients admitted to the hospital at Exeter for treatment of the disease.

September, 1762, to September, 1763 ..	72
September, 1763, to September, 1764 ..	75
September, 1764, to Lady Day, 1766 ..	86
Lady Day, 1766, to July 6, 1767	52
	285

Dr. Andrew adds that " the most violent symptoms of this disorder, such as pain and costiveness, are generally removed, before the sick are brought to the hospital ; and that nothing commonly remains but a paralytic weakness in the arms ".

After a series of chemical investigations Baker concluded that the mischief arose in the vats.

> " The large circular trough, in which the apples are ground, is generally composed of several pieces of moor-stones, cramped together with iron, some melted lead being poured into the interstices. It frequently happens that these stones, which are thus to be joined, are unequal, and do not correspond with each other ; so that considerable chasms are filled up with lead. In this case the apples, ground by the pressure of the roller, immediately come in contact with no small quantity of this poisonous mineral."

Dr. Thomas Percival, perhaps best remembered for his work on the Manchester Board of Health, in 1773 added to the literature on lead poisoning. He emphasized that the deleterious effects were not confined to man but affected quadrupeds and birds. Furthermore he cited several cases in which he was of opinion that the disease had resulted from external applications of such medicaments as extractum saturni of Goulard and saccharum saturni. He also observed and collected the experience of local practitioners on the occurrence, symptoms and treatment of the *colica pictonum* among Derbyshire lead miners—particularly smelters—and among the manufacturers of white and red lead works in Sheffield. A practitioner of Bakewell in Derbyshire contributed the following account :

> " The men first complain of a weight, pain of the stomach and costiveness, which are generally relieved, if they apply early for advice, by a vomit, and pills of soap, rhubarb and aloes ; or by any aperient medicines of the liquid kind, with oil added to them. But if these symptoms be neglected, the patients complain of their saliva becoming sweet, of clammy sweats, lassitude, feebleness of the legs, a total loss of appetite, obstinate costiveness, and a fixed pain in the abdomen, with severe retchings. In this stage of the disorder, oily clysters and gentle purgatives are the most effectual remedies ; and are usually repeated at short intervals, till the stools assume a natural appearance. For during the disorder they are hard, dry and scaly like bran. The oleum ricini has of late been used with great success."

Both as a prophylactic and as a remedy in slighter cases of the colica pictonum Percival recommended small frequent doses of alum, from which he had observed good effects. The following is of interest :

> " In Derbyshire, when miners or smelters of lead find themselves affected with the asthma they usually leave their occupation for a while, and work at the lime kilns, experience having taught them that the fixed air, or *mephitis*, arising from the calcination of lime stone, is an effectual and speedy remedy in this disorder . . . Men employed in burning lime are remarkable for their health and longevity. This observation is the result of more than thirty years' experience ; and perhaps may corroborate the popular opinion, that in consumptions of the lungs it is good to live near places where this process is carried on."

In view of this reference to asthma, which might suggest the occurrence of fibroid phthisis or silicosis, it may be worth while noting that the lead ore in Derbyshire occurs in limestone strata.

Dr. Rotherham of Newcastle-upon-Tyne in a letter to Percival recounted his experience of lead poisoning among lead miners and smelters in Hexham, where he had formerly practised. The workmen knew the disorder as the mill-reek. The effluvia rising from the works caused the belland in cattle and, as he records, neither dogs, cats nor poultry could thrive in the neighbourhood of the mills.

A letter headed Manchester, October 27th, 1678, from Dr. John Carte to Dr. Grew and extracted by Percival from Dr. Hooke's Philosophical Experiments published by Mr. Derham, F.R.S., gives an account of a distemper which was very common among workmen employed in smelting mills, that is the houses where they melt the lead down from the ore, in Derbyshire. The account is a description of the belland as it affected men and other creatures.

In the course of his investigations Percival made a series of experiments. He records that " the very beautiful polish of the Burslem pottery, commonly called the Queen's ware [the most celebrated domestic tableware (earthenware) made by Wedgwood], inclined me to suspect that lead, which is easily vitrified with sand and Kali, enters into the composition of its glazing ". After a series of tests he found that lead was an ingredient in the glaze. The amount, however, was small and so he concluded :

> " The present experiment, therefore, furnishes no objection to the common use of this beautiful pottery ; but it shews that vessels of it are improper for the preserving of acid fruits and pickles."

Almost simultaneously Dr. Gouldson of Liverpool published a pamphlet on the subject of " earthenwares Glazed with Lead ".

Wedgwood (1773) in his letters to Bentley alludes to these papers. While Queen's ware was exonerated from blame he felt that " when ignorant people read an account of lead and poison and Queen's ware in the same paragraph they might associate the ideas together . . . and never after see one of our plates without the idea of being poisoned by it ". However, he decided not to engage in controversy with the learned doctors but on a wiser course : " I will try in earnest to make a glaze without lead, and if I succeed will certainly advertise it ".

And so from these now remote days down through the centuries medicine has continued indivisible ; the quest for the cause of disease towards its ultimate prevention ; the alleviation of the effects in the patient ; the investigation of the related environmental and social problems and always, as enunciated by Dr. Huxham, " sine experientia, vana omnis theoria, bella sit utcunque ". Finally there is the unique contribution, as here illustrated, of the general practitioner, who, close to the people, has unlimited opportunities to advance the frontiers of medical and social science to the well-being of all.

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MISCELLANEA

Beryllium Granuloma of the Skin*

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Granulomatous lesions of the skin produced by beryllium compounds were first described by Grier, Nash, and Freiman (1948), but no case occurring in this country has yet been published. As interest in the effects of exposure to beryllium has grown with the increased use of this metal during the last decade, a case of multiple beryllium granulomatosis of the skin occurring in a girl of 20 years is described.

The patient was employed in a factory making fluorescent tubes. The makers of the tubes informed us that the fluorescent powder used at the time of the injury consisted of a mixture of zinc beryllium silicate with an average beryllium content of about 8%.

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Splinters from a broken tube penetrated the hands and feet. The small wounds healed with simple treatment and it was four years later when she attended as an outpatient complaining of lumps at the sites of injury. There was no pain.

On examination there were four granulomatous nodules at the sites of injury, two of which were slightly ulcerated (Figs. 1, 2, 3, and 4). The largest of the lesions on the plantar surface of the left foot measured about 2 cm. in diameter. There was no tenderness. Radiographs of the chest and small bones of the hands showed no abnormality. A Mantoux test was negative.

The lesions were excised and she made a complete recovery.

Histology of the Lesions

The lesions involved the skin and the underlying fat tissue and showed considerable structural variety. In some sections (Fig. 5) the nodule was made up of numbers of discrete or confluent granulomata, each consisting of compact collections of mononuclear epithelioid cells surrounded by scanty lymphocytes and

FIG. 1

FIG. 2

FIG. 3

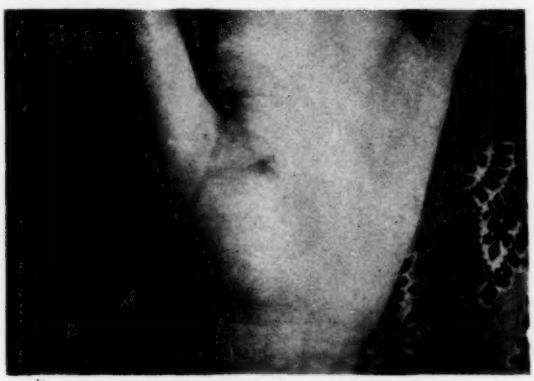

FIG. 4

FIGS. 1–4.—Granulomatous nodules of the hand and feet, and ulceration (FIGS. 2 and 3).

FIG. 5

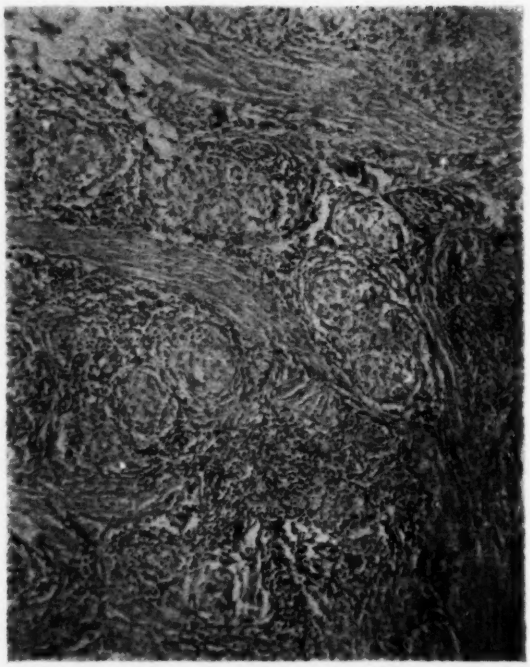

FIG. 6

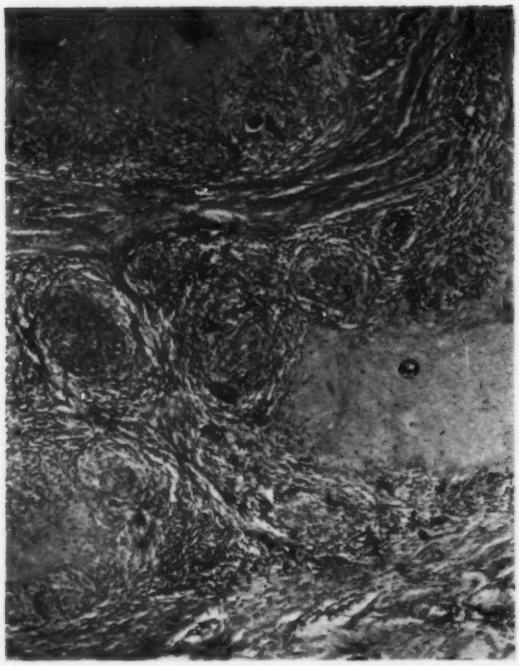

FIG. 7

FIG. 8

FIG. 5.—Lesion on the hand showing a sarcoid-like granuloma × 38.

FIG. 6.—Sarcoid-like granuloma from lesion of foot × 70.

FIG. 7.—Extensive caseation : one foreign body with adjacent giant cell is present in the outer rim of a granuloma, another near the centre of a caseous focus × 47.

FIG. 8.—Same as Fig. 7, showing the granular foreign body lying in an empty space × 260.

including a very few giant cells of either Langhans or the foreign-body cell type. There was considerable condensation of the areolar tissue separating single or groups of granulomata, a very few of which showed a mild degree of central caseation. This picture (Fig. 6) is indistinguishable from a typical sarcoid lesion. In other lesions, in addition to these changes, there was extensive caseation of confluent granulomata (Fig. 7). Conchoidal bodies were not found in any of the slides. The epidermis over the different nodules showed various degrees of atrophy, ulceration, or hyperkeratosis. Serial sections failed to show foreign bodies in most of the examined material, but in one of the lesions which had not ulcerated small granules of refractile but polariscopically inert material were found within the necrotic zone and also at the periphery of a granuloma (Figs. 7 and 8). Sections were stained by Denz's (1949) naphthochrome G method to detect beryllium histochemically. Negative results were obtained in material void of foreign bodies, but in sections containing the refractile granules there was a faint but diffuse positive histochemical reaction. In one area, where the granules had been lifted out in the cutting, a narrow, greenish rim surrounded the hole.

Spectrographic examination of the material for the presence of beryllium gave negative results. As cases have been reported in the literature of sarcoid-like lesions in the skin following road accidents which have been attributed to the presence of silica in the road dust, the biopsy specimens were also examined spectrographically for silica. All portions of the samples contained silica in low concentration but the silica content of normal and abnormal tissue did not vary appreciably.

Finally, in order to determine the nature of the granular material, sections were incinerated at 500° C. It was found that the material was still present after exposure to heat. Treatment with hydrochloric acid after incineration resulted in the particulate matter disappearing.

Review of the Literature

VanOrdstrand, Hughes, DeNardi, and Carmody (1945) in describing toxic manifestations resulting from exposure to beryllium mentioned one patient who developed a chronic skin ulcer from traumatic implantation of beryllium. Chronic lesions in the skin, cut with broken fluorescent lamps coated with beryllium containing phosphor, are described by Grier and others (1948) and compared with identical cutaneous manifestations in two patients suffering from pulmonary beryllium granulomatosis. Beryllium was demonstrated spectrographically in one of these lesions. Coakley, Shapiro, and Robertson (1949) describe a beryllium granuloma of the skin occurring in a boy of 16 years, two years after injury to the face by a broken fluorescent bulb. Gerrie, Kennedy, and Richardson (1950) report a similar case after injury to the forehead, and Ormsby and Ebert (1950) a granulomatous lesion following an accidental cut of the finger by a broken fluorescent bulb. The other toxic manifestations of beryllium have been reviewed by Vorwald (1950) and Hardy (1951).

Experimental Beryllium Poisoning

Gardner and his successor Vorwald (1950) at the Trudeau Foundation tested various beryllium compounds on a number of animal species by intravenous, intraperitoneal, subcutaneous, and intratracheal injections and obtained tissue reactions in no way comparable to the human lesion. Neither did inhalation experiments with fluorescent powders reproduce the type of human tissue reactions. It was found, however, that some of the injected beryllium compounds proved highly toxic even in small amounts. Aldridge, Barnes, and Denz (1949) studied the effects of a large number of beryllium compounds injected intravenously and subcutaneously into rats and mice. They concluded that beryllium ions have the property of reacting rapidly with tissue protein to form a stable beryllium protein complex which still retains the toxicity of the beryllium. This would explain the localized tissue reaction following implantation or inhalation of beryllium salts. Stokinger, Ashenburg, DeVoldre, Scott, and Smith (1950) using beryllium sulphate mist in inhalation experiments were able to produce pulmonary lesions resembling those of acute pneumonitis of beryllium workers, but did not obtain tissue reactions comparable with the granulomatous type. They further showed by alternating daily exposures to beryllium sulphate mist and hydrogen fluoride vapour that fluoride enhanced the toxicity of the inhaled beryllium. The same group of workers, Hall, Scott, Laskin, Stroud, and Stokinger (1950) investigated by inhalation experiments the action by four grades of beryllium oxide dust varying in particle size and state of aggregation. They found that the smaller the particle size and the lesser the degree of aggregation the greater was the injury to the lungs. On the basis of these findings Dutra (1951) produced granulomata in pigs after implantation into the cutis and the subcutaneous fat tissue of fluorescent powders containing zinc oxide, beryllium oxide, and silica in equal molecular ratio and of average particle size of 1·5 and 3·0 microns respectively. The author failed, however, to produce granulomata with metallic beryllium or beryllium oxide alone. It is interesting to compare these results with the experiments of Lloyd Davies and Harding (1950) who produced cellular pulmonary granulomata after intratracheal injection into rats of a mixture of beryllium oxide and manganese dioxide. Davies and Harding concluded that granulomata may form only when the action of the beryllium is reinforced by some other agent or agents provoking histiocytic proliferation.

Conclusion

Sarcoid-like skin lesions following implantation into the skin of fragments of broken fluorescent bulbs, histologically identical or similar to pulmonary changes found in chronic pneumonitis of workers engaged in the beryllium industry, have been attributed to the beryllium in the coating of these lamps. In our case multiple injuries caused by particles from a broken tube, coated with a fluorescent powder containing zinc beryllium silicate, resulted in the formation of typical granulomatous lesions. Histochemical examination of the

affected tissue indicated beryllium as present in traces. Spectrographic analysis by a method capable of detecting one part of beryllium in one hundred million (10^8) parts of tissue failed to demonstrate it. Results of incineration were inconclusive. Silicon was present in identically low concentrations in normal and granulomatous portions of the skin and it is thought that this amount could easily be due to pick-up from storage of the specimens in glass containers.

The negative results of chemical analysis are inconclusive since it is probable that the chemical substance implanted into the skin has disappeared in the interval of four years following the trauma.

Summary

A case is described of multiple granulomatous skin lesions resembling Boeck's sarcoid following traumatic implantation of fragments of a broken fluorescent bulb coated with zinc beryllium silicate.

Histochemical and spectrographic examination failed to prove that beryllium was the causative agent.

We wish to thank Dr. F. A. Denz for his help with the histochemical staining of sections ; Dr. E. H. Harding for incinerating sections ; Mr. L. C. Thomas for carrying out the spectrographical examination of the material.

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First Conference of the British Occupational Hygiene Society

The first conference of the British Occupational Hygiene Society was held at the London School of Hygiene and Tropical Medicine on November 2, 1953. The Dean of the School, DR. A. TOPPING, welcomed the Minister of Labour and National Service, the RT. HON. SIR WALTER MONCKTON, who said :

As the Minister whose department is responsible for administering and developing the laws for securing the health, safety, and welfare of more than 7 million workers in factories and other premises subject to the provisions of the Factories Acts, I am happy to help in the inauguration of a society which brings together scientists and others who have duties and who possess expert knowledge in this particular field of work. The prominence now being given in Government and other quarters to the development of provision for occupational health in its widest sense shows that occupational hygiene is a subject which will receive increasing attention. Occupational hygiene is positive, not concerned only in preventing recognizable diseases : its business is in maintaining full bodily efficiency, well-being, and safety. It is particularly opportune that the foundation of this Society should come at a time when efforts are being made to establish and develop this important service to industry.

Your members, in their various capacities, will be able to give much corrective advice on many of the problems which will arise. You will know that my Ministry is particularly concerned with human relations in industry. Industrial progress is dependent more than anything else on the human element in industry—on the health, well-being, and good will of managements and their workers. The application of knowledge of practice of many kinds is necessary to attain these objects. The medical profession, the physiologist, and the psychologist must work hand in hand with the engineer, the chemist, and the physicist, and a vital factor must be the closest collaboration between industrial research and industrial health research. Occupational hygiene involves study of the reactions of man to his environment. The physician, the medical scientist, and the psychologist study man : the physical scientist (and he includes the engineer) is concerned with man's environment. It is by the harnessing of these different elements that I look for enduring achievements by your Society.

Industrial hygiene has always been a matter of first importance in the work of my Factory Inspectorate. Quite apart from special requirements in Regulations dealing with those industries and processes where specific types of occupational disease and poisoning are likely to occur, the Factories Act aims at preventing the ordinary ailments, and not merely those which are unquestionably industrial in character and origin. It is not without significance that the opening sections of that Act relate to matters of hygiene, to provisions about cleanliness, overcrowding, ventilation and temperature, lighting, and so forth, and that a later part of the enactment deals with washing facilities, cloakroom accommodation, protective clothing—all within the subject dealt with by your Society.

It will be generally agreed that the number of chills and colds avoided, or indeed the amount of positive health resulting from such provisions, whilst not capable of such statistical statement, must be very considerable indeed. In the incidence rates of cases of notifiable occupational diseases a broad picture of progress and the effect of applying the principles of occupational hygiene can be obtained. Take, for example, the case of lead poisoning. In 1900 there were 1,050 cases of lead poisoning in industry in this country, of which 38 ended fatally, whilst in 1952 there were only 48 cases, none of them fatal, with a greater number of employed persons at risk. At present notifiable industrial diseases scheduled under the Factories Act are classified under 14 different headings, and the total number of cases in all these classes was 594—not much more than half of the number of lead poisoning cases at the beginning of the century. The small numbers now appearing in the tables of industrial poisoning cases published each year in the Report of the Chief Inspector of Factories indicate to what extent precautionary measures which constitute the practice of occupational hygiene have been successful in the past. But these results must not be regarded as an excuse for complacency, and much work lies ahead.

During the last decade there has been a marked increase in the interest shown in health matters by industry, but it cannot be said that the facilities for studying occupational risks to health have kept pace with the growing awareness of the importance of this subject. The establishment of your Society should provide a means of arousing a greater interest in occupational hygiene by focusing attention not only on the medical aspects of its practical application, but also on the engineering, chemical, and physical nature of many of its problems. If progress is to be obtained in industrial health, everyone in industry has some contribution to make, and joint and sustained effort is required. It was with this object in view that Ernest Bevin, in 1943 when he was Minister of Labour and National Service, called together a conference on industrial health, which was addressed by experts from the broad and varied fields concerned. As a result of this, advisory panels were set up to advise the Factory Department on dust hazards, dermatitis, ophthalmology, radiology. The members of these panels came from industry, medicine, science, and Government departments, and as Minister I am indebted to the work which they have done.

One of the pressing demands in industry at the present time is the need for people, suitably qualified to apply principles of health and safety, which are closely interwoven and closely concern the welfare of the industrial worker in his factory environment. Occupational hygiene is thus one of the subjects which should be introduced into the essential training and education of all concerned with these matters, in order that the doctor, engineer, scientist, or personnel officer may recognize

occupational hazards and realize that each has a contribution to make towards the preventive methods which ought to be adopted. This applies equally in the field of research. Whilst the primary aim of most industrial research is quite understandably concerned with discovering new and improved methods of production, it is important that principles of hygiene should be fully understood and practised by research workers, so that the safest and healthiest methods and designs may be incorporated into new plant at the pilot stage. Joint consultation between those carrying out industrial research and those responsible for occupational health is essential before any new project is put into production.

It is self evident to those who study human problems that using our man power to the best advantage means a great deal more than just seeing that the right man is in the right job, important though that is. Above everything else, it means understanding men and women, understanding things that influence their attitude to their daily work and to one another. We want to know a great deal more than we do at present about the things that release the full measure of human resource and enterprise, about the relationship between incentive and environment, and the extent to which environment can enhance the effectiveness of the group—in short about those human factors which will be the particular study and concern of your Society. The field of your enterprise is very large indeed, and I am sure that you will have much to contribute to our present knowledge of the things that make for greater satisfaction and, consequently, greater happiness.

I have a special pleasure in being here today in that I can personally congratulate you on the choice of your first president, Dr. Bedford. He has long been known as an international authority in special fields of environmental hygiene. For many years he has advised the Factory Department of my Ministry, and many of my inspectors have had cause to remember his teaching in the sciences of heating and ventilation. Members of the House of Commons have a particular reason to be grateful to him. His work in balancing the heating and ventilating system in the House can only be appreciated by those who had previously to endure blasts of hot and cold air from all sections of the House with bewildering frequency.

Although this Society of yours with its special aims and objects is new to this country, there is a well known body in the United States, and I am sure that we are all delighted that the American Association is represented here today by Dr. Henry F. Smyth Jr. As is our custom, we accept innovations with caution until the need is evident. The founders of this Society have followed this principle and have given much thought to its constitution and to the qualifications for membership. Membership is not limited to scientists, as you know, but may include others with interests and responsibilities in the wide field of occupational health. In this way, scientists and industrial doctors and others may contribute their gifts and knowledge to the common purpose. In my Ministry, we have, in the Factory Department, direct experience of this sort of team-work between the various professions concerned, and I am convinced that it is the right way of working.

In the Ministry of Labour we shall watch your progress with lively interest and I wish you every success in the important tasks that lie ahead.

Occupational Hygiene in Great Britain

THOMAS BEDFORD

It is no new discovery that health is affected by occupation, nor is it only in recent times that occupational hygiene has been practised.

The writer of *Ecclesiasticus* described the work of various craftsmen. He wrote :

> " The smith also sitting by the anvil, and considering the ironwork, the vapour of the fire wasteth his flesh, and he fighteth with the heat of the furnace : the noise of the anvil is ever in his ears, and his eyes look still upon the pattern of thing that he maketh : he setteth his mind to finish his work, and watcheth to polish it perfectly."

He also gave a graphic description of the work of the potter. These passages reveal a clear realization of the stresses imposed by occupation.

Again, four centuries before the Christian era, Hippocrates alluded to the difficult breathing of the metal digger.

In the sixteenth century Agricola referred to the perilous nature of mining because of the dust which caused asthma, and at times produced consumption. On that account, in the Carpathian mountains there were women who had married seven husbands, all of whom miner's consumption had brought to an early grave.

Perhaps the first reference to the application of preventive measures in industry goes back to Roman times, when Pliny mentioned that men refining cinnabar enveloped their faces with loose bladders so that they could see without inhaling the fatal dust.

Development in Great Britain.—The history of the application of industrial hygiene in this country in more modern times is largely reflected in the industrial legislation of the past 150 years.

The introduction of power-driven machinery in the latter part of the eighteenth century made it possible for a child to perform tasks which had previously required the strength of an adult. This encouraged the exploitation of child labour, particularly in the textile mills of the north. Very young children, especially those indentured under the Poor Law, were required to work long hours, and often at night, in unhealthy surroundings. Following an outbreak of fever in the cotton mills around Manchester towards the close of the eighteenth century, there was agitation for the regulation of the working

conditions of these children, and probably as the result of this there was passed the Health and Morals of Apprentices Act of 1802. This Act, an extension of the Poor Law, marked the beginning of factory legislation. It limited the hours of work of Poor Law apprentices to 12 a day and forbade night-work ; and it required that factories should be whitewashed twice a year, and properly ventilated. Further Acts of 1819 and 1831, which applied only to cotton mills, prohibited the employment of children under 9 years of age, and applied the 12-hour day to all under 18.

The limitation of the hours of work of children was extended throughout the textile industries by the Act of 1833. This Act also provided for the appointment of Government factory inspectors, and for certificates of age to be given by medical men—the first suggestion of certifying surgeons.

Up to 1842 women and children were employed in mines, often under bestial conditions. The Mines and Collieries Act of that year prohibited the employment underground of women or of boys under 10 years of age, and provided for the appointment of inspectors of mines.

Two years later women factory workers were included in the limitation of hours of work, and later legislation extended protection to workers in other industries and imposed some further limitations of hours.

In 1844 there was enacted the first requirement for the fencing of mill-gearing and shafting, and more than 20 year later, in 1867, the safety provisions were extended to require the fencing of machinery.

The year 1864 saw the first provisions for the prevention of industrial poisonings. The taking of meals in certain rooms where noxious materials were handled was forbidden, while employers were given power to make special rules for dangerous trades ; and in 1867 the removal of dangerous dust by mechanical means was first required.

Lead poisoning was dealt with in an Act passed in 1883. In 1891 power was given to control dangerous trades, to prohibit dangerous processes until they were made safe, and to prohibit or restrict employment in trades certified to be dangerous. In 1895 medical practitioners were required to notify certain industrial poisonings.

In 1889, and later, provision was made for regulating humidity and ventilation in cotton cloth factories.

The Consolidating Act of 1901, which remained in force until 16 years ago, brought further advances.

From this it is clear that the emphasis in the early years was on the protection of children, and later of young persons and women, from the evils of gross overwork. Such conditions had played havoc with the health and physique of the industrial population. Yet the protective laws were not made without a struggle, for during the first half of the last century there was bitter controversy, even after Orders in Council had restricted the hours of labour of slaves, adult and child, in British possessions overseas.

Attention to safety from injury, and from industrial poisonings, came later, and the progress in that direction was due to the initiative and devotion of the Factory Inspectorate.

From the standpoint of occupational health, a notable event in the history of the Factory Department was the appointment in 1896 of a medical man, Dr. Whitelegge, as Chief Inspector of Factories. This was followed, two years later, by the appointment of the first Medical Inspector of Factories, Dr. (later Sir) Thomas Legge, to whom industrial hygiene in this country owes an immeasurable debt.

The Factory Department waged war on industrial diseases which had earlier killed many workers. Thus, while research on silicosis was yet in its early stages, great reductions were effected in the death-rates from grinder's phthisis and potter's rot through the application of industrial hygiene measures.

There was still no agency for research in occupational hygiene, however. Such research as was accomplished was done by various people, including factory inspectors, who were already laden with other duties.

Then came the first World War. Early in 1915, the Ministry of Munitions was set up to combat the serious shortage of war supplies. Meanwhile, in the effort to make good the shortage, factory workers worked for such long hours, over so long a period, that output declined, and the health of the people suffered. Not uncommonly people were working 80 to 100 hours a week. These effects caused much concern, and the Minister of Munitions appointed the Health of Munition Workers Committee to consider and advise on questions of industrial fatigue, hours of labour, and other matters affecting the health and physical efficiency of munition workers.

In its Interim Report, published in 1917, the Committee said :

> " Our national experience in modern industry is longer than that of any other people. It has shown clearly enough that false ideas of economic gain, blind to physiological law, must lead, as they led through the 19th century, to vast national loss and suffering."

In its Final Report, issued in 1918, the Committee stressed that efforts to protect the health of workers had been based mainly on the need for mitigating or removing admitted evils as they arose. The Committee expressed the view that it was necessary to make arrangements without delay for a national scheme of industrial medical research, and to accord fuller recognition to the importance of industrial hygiene.

Shortly after the dissolution of the Health of Munition Workers Committee in 1918 the Industrial Fatigue Research Board was set up under the joint auspices of the Medical Research Committee and the Department of Scientific and Industrial Research to study the relation of methods and conditions of work to functions of the human body, having regard both to the preservation of health and to industrial efficiency. The appearance of the word " fatigue " in the title of the Board is a reflection of the importance then rightly attached to the problems of hours and methods of work. In 1921 the Board was taken over entirely by the Medical Research Council, as it had then become, and later, when the emphasis on

the various aspects of its work had shifted, its title was changed to the Industrial Health Research Board.

Research bearing on occupational hygiene was also carried out by other organizations, including the Safety in Mines Research Board, the Building Research Board, the National Physical Laboratory, and, of course, the Factory Department and some university departments.

The Second World War gave a further impetus to research in occupational hygiene, partly in connexion with the war industries, and partly on behalf of the fighting services; and since the war ended there have been further developments. Many research units of the Medical Research Council are working on problems in this field, and much research effort is being put forth by the National Coal Board and the Ministry of Fuel and Power. Some of the industrial research associations also include hygiene problems in their research programmes.

The Scope of Occupational Hygiene.—It is well for us to look backwards sometimes and to appreciate and acknowledge the work done by our predecessors, who accomplished much in spite of great difficulties, much discouragement, and less powerful research methods than are now available. Yet this is a new Society. We are concerned with the present, and with the future, wherein lie our hopes, and I must turn to discuss the scope and objects of modern occupational hygiene.

Hygiene is "that branch of knowledge or practice which relates to the maintenance of health". Health, in turn, is defined as "soundness of body: that condition in which its functions are duly and efficiently discharged".

Occupational hygiene is not concerned only with the prevention of recognizable diseases, whether of specific occupational origin or otherwise. Its business is the maintenance of full bodily efficiency, well-being, and safety.

Of course, the prevention of industrial diseases is an extremely important part of occupational hygiene. These diseases are preventable and they should therefore be prevented. Indeed, to a large extent they are prevented, for without the vigilance and control that are already exerted their toll would be far heavier than it is today. But even so, that toll is by no means insignificant. The pneumoconioses alone annually cost the community large sums by way of compensation, and much loss of production, while to the victims and their families they bring misery.

The bulk of industrial sickness does not find its origin in the so-called dangerous trades. Most trades are not dangerous, in the sense in which the expression is commonly used, but there is the strongest evidence that rates of sickness and mortality are materially affected by occupation. It is one of the tasks of occupational hygiene to seek out and remove the causes of this excess of sickness.

Besides the prevention of recognizable illness, occupational hygiene is concerned with the application of physiological laws to the management of work. It includes the study of the effects of the working environment, and is thus concerned with the control of temperature and humidity, and the ventilation of the workplace: with lighting and noise, and, nowadays, with the control of exposures to radio-active materials. It also includes the application of physiological and anatomical principles to the arrangement of industrial tasks, the design of machines, and the arrangement of work-spells. Health and efficiency are greatly influenced by psychological factors, such as fatigue and boredom, especially in repetitive work, and maladjustment of the worker either to his vocation or to his working group. Such psychological matters as these must therefore be regarded as falling within the scope of occupational hygiene.

I should here refer to the reason for the use of the expression "occupational hygiene" in the name of our Society, instead of "industrial hygiene", which term has been commonly used in the past.

Agriculture is our oldest industry, but one often hears the expression "agricultural and industrial workers" as though agriculture and industry were separate divisions of labour. Especially in these days when toxic insecticides are widely used, agriculture has its own hygiene problems, and it should be within the power of this Society to help in their solution. Moreover, the fighting services have their hygiene problems, some similar to those of industry and others peculiar to the Services, or to a particular Service. We wanted to be free to discuss Service problems insofar as the requirements of security permit, and it was therefore logical to use the adjective "occupational" instead of the more restrictive "industrial".

Teamwork.—Occupational hygiene requires the employment of many skills, embracing those of the various branches of medical science, the physical sciences, and engineering. Its research problems call for the work of highly skilled chemists, physicists, petrologists, engineers, physiologists, and psychologists, as well as that of physicians and pathologists; and most of these need to acquire much of the skill of the statistician.

The practical application of the results of research work in industry also calls for skill, insight, and often ingenuity, on the part of the industrial health engineer or other person on whom that duty falls.

In both research and its application occupational hygiene calls for teamwork. That is quite evident, for men are not omniscient. There are occasions when an individual worker can get along very well under his own steam. But neither the physician nor the lay scientist will get very far without the cooperation of the other, and for work on major problems persons trained in various disciplines will be needed.

As my friend Professor Hatch put it in his Cummings Memorial Lecture to the American Industrial Hygiene Association two years ago, one can think of occupational hygiene as a joint field of specialization. The activities of the various specialist professions engaged in it are characterized by interdependence, mutual support, and

teamwork. And, Professor Hatch added, in importance these transcend the separate skills and special techniques, valuable as they are.

In that admirable lecture Professor Hatch gave a brilliant exposition of the concept of teamwork in industrial hygiene, and I commend it for your earnest consideration.

The cardinal point is that we are primarily concerned with the reactions of man to his environment. Broadly, the physician, the medical scientist, and the psychologist are concerned with man, while the disciples of the physical sciences, including the engineer, are for the most part concerned with the environment. It is from the linking together of the two sides of the work that one arrives at an understanding of the man-environment relationship.

In an occupational hygiene team, as in any other, mutual understanding is necessary for success. Aside from personal relationships, those working together must know something of each other's work. Each must understand the language of the others, and be aware of the potentialities and limitations which confront them. The physicist and the engineer must appreciate the lack of precision which is often inherent in biological assessments, whether these are clinical appraisals or estimations of biological samples, and in turn the medical man must know the difficulties which beset the physicist or the chemist in sampling, or the engineer in effecting desirable controls.

Although each member of the occupational hygiene team should know something about the work of his colleagues, and may on occasion find himself having to undertake work which might more appropriately have been done by others, there is much to be said for the cobbler sticking to his last.

Here I feel constrained to hazard a word about education in industrial hygiene as far as this country is concerned.

There are in Great Britain university departments which have provided courses of study for the medical post-graduate Diploma in Industrial Health. In some of these departments short courses of lectures have been given which non-medical people could attend. Yet there is no university in this country which offers a full course of instruction in occupational hygiene for engineers and other non-medical people comparable with the teaching provided by some American universities, and notably those of Harvard and Pittsburgh. It seems to me that this is a serious lack.

Nor do I feel that all is well with respect to the training of medical men for work in industry. The Diploma in Industrial Health is a valuable qualification, which calls for a sound knowledge of industrial medicine, but I doubt whether it requires an adequate knowledge of methods of assessing and controlling the working environment. Dr. Merewether has said that the industrial doctor should learn about industrial health as a whole. His training must bring him knowledge of the working environment and of industrial processes.

Responsibility in Occupational Hygiene.—There can be little doubt that from the material standpoint the general standard of living has been raised since the Industrial Revolution, but has that brought more happiness? Too often in this mechanized age men find themselves mere cogs in a massive and unfeeling machine.

Marvellous advances have been made in the development of machinery and industrial processes, but often at the expense of no longer needing skilled craftsmen and requiring instead just "hands". Man-management has been found wanting, and men tend to rebel against what, rightly or wrongly, they regard as a soulless machine. Surely enlightened and understanding management can remove some of these difficulties. Indeed, it has done so in some large undertakings.

Frequently, success in the application of occupational hygiene cannot be measured in terms of increased output per man-shift, important as that may be from the standpoint of industry, but rather in terms of improved health and happiness. The tendency to measure success in terms of output may give an impression of complete callousness.

Some years ago, in a paper on mechanization in coal-mines, there appeared a discussion of the basis of the calculation of accident frequency rates. The author advocated the use of rates showing the number of accidents per million tons of coal mined, and said that, provided the rates so calculated declined, he would not object to increases in the rates calculated on the basis of man-shifts worked or persons employed. It is cold comfort to the individual miner that the compensation costs per ton of coal are reduced if, while that result is achieved, the risk to him is increased.

There are various statutory requirements of employers in connexion with occupational hygiene. But industry should provide higher standards than the bare minima which will just suffice to avoid prosecution.

The industrial worker should be able to earn his daily bread without undue risk of physical injury and without risk of poisoning through the inhalation of toxic substances or other contact with them. I have said earlier that industrial diseases are preventable and should therefore be prevented. They should be prevented even though the necessary measures may be costly; and the safeguards should not impose hardship or serious and prolonged discomfort. Thus, it is iniquitous to demand of a worker that he wear a respirator as a matter of routine unless other safeguards are quite impossible. The wearing of a respirator in this way constitutes a confession by management that it has failed to deal adequately with the situation. The worker should not be exposed to unnecessary risk in order that the product of his labours may be sold more cheaply. Life is not cheap.

Methods of work, machines, and the working environment should be such as not to impose undue strain. The intelligent application of the results of physiological research can do much to ease the load on the worker, and to improve his efficiency.

Understanding management, which gives leadership

and treats the worker as a person and not merely as a productive unit, can do much to bring contentment and at the same time increase production.

The worker, also, has his responsibilities. Where means of protection against personal injury are provided he should use them. Where certain acts are prohibited in the interests of safety he has a strong moral, as well as a legal, duty to refrain from them. Otherwise he may endanger the lives of others as well as himself.

Without the full cooperation of the worker full success is unlikely, but the major responsibility rests with the employer. In that connexion I quote two axioms laid down many years ago by Sir Thomas Legge :

(1) " Unless and until the employer has done everything—and everything means a good deal—the workman can do next to nothing to protect himself, although he is naturally willing enough to do his share.

(2) All workmen should be told something of the danger of the material with which they come into contact and not be left to find it out for themselves—sometimes at the cost of their lives."

The scientist should not offer industry new processes or materials, nor should industry accept them, without first ensuring that they are unlikely to cause injury to health.

The full cooperation of the trade unions is necessary. They should seek for good conditions of work rather than for " danger money " to compensate for bad.

The full achievement of the aims of occupational hygiene calls for the devoted work of scientists, cooperating with each other and with industry, in seeking for a fuller understanding of the relation between man and his environment, and in endeavouring to remove any hazard to health with all speed, once it has been recognized, even though the perfect method of assessing the hazard may not yet have been found. Such research is likely to be arduous and often prolonged, and it may not bring resounding fame to the researcher but he will be making his contribution towards the welfare of mankind.

Finally, a yet stronger sense of mutual obligation is needed, so that employers will seek to provide healthful conditions as a moral duty, while employees will readily use the means of protection provided, as a duty to themselves and to their fellows.

So, health and happiness may be promoted, and, I believe, material prosperity increased.

DR. HENRY F. SMYTH, President of the American Industrial Hygiene Association, conveyed formal congratulations and best wishes and presented the Society with a gavel on behalf of his Association.

Measuring the Workers' Environment

S. A. ROACH

From the Pneumoconiosis Research Unit of the Medical Research Council, Llandough Hospital, Nr. Cardiff

Although harmful materials may enter the body by ingestion with food or by absorption through the skin, in many industries their most important mode of entry is by inhalation. The material may, like poisonous gas, be immediately dangerous, or its effects may be the result of the accumulated exposure of a life time. The problems arising in determining the risk to health by means of measurements of the environmental conditions may appear at first sight to be very different, but I hope to show in this paper that they are actually very similar, if not identical.

The Period of Accumulation

A substance may enter the respiratory tract in the form of solid particles or liquid droplets or as a gas. Solid particles and liquid droplets are deposited on the upper respiratory tract, the coarser particles being deposited first and the finer particles sedimenting out in the deeper parts of the tract. If they are not immediately dissolved the coarser particles are removed by ciliary action and may subsequently be swallowed. The finer particles which have been deposited in the alveoli may remain in the lungs indefinitely if they are insoluble, so that the amount of dust in a man's lungs is roughly proportional to the product of his age and the average concentration of dust to which he has been exposed since birth.

On the other hand a relatively soluble dust such as lead is absorbed in the lungs so that it fairly rapidly accumulates in the blood, tissues, and skeleton, and is eventually excreted. The rate of solution increases with the amount of material deposited in the lungs and the rate of excretion of the material increases with the amount in the body, so that under exposure to a constant concentration a level of equilibrium will eventually be reached when the amount in the body is such that the rate of excretion just equals the rate of deposition in the lung.

In contrast to coal and silica, the lead in the body is slowly excreted when exposure ceases and the lead content usually reaches normal values within about 18 months (Kehoe, Thamann, and Cholak, 1933). Thus the amount of lead in the body is determined by the level of exposure over the previous 18 months and, to a great extent, by that within the previous few weeks.

The period of accumulation is even shorter in the case of harmful gases. Both absorption and elimination take place in the lungs, and, once the blood becomes saturated, accumulation in the rest of the body (when it takes place to any significant extent) is dependent on the concentration in the blood. For example, with a vapour such as benzene, saturation of the blood is reached within a few minutes ; and saturation of the tissues is reached in two or three days (Schrenk, Yant, Pearce, Patty, and Sayers, 1941).

These points are illustrated in Fig. 1. The top half of the diagram indicates the situation in which a man is exposed to a constant atmospheric concentration of the

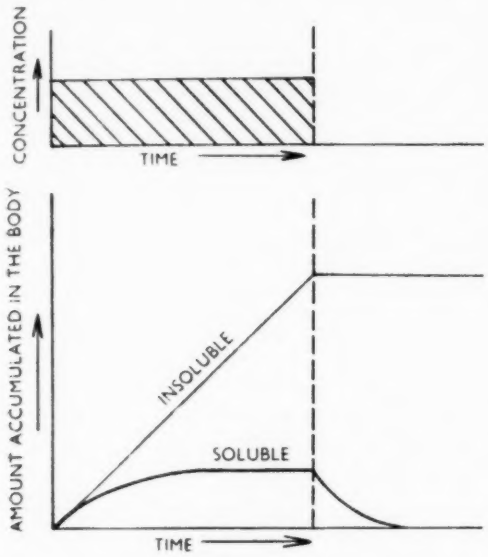

FIG. 1

material for a given length of time. The bottom half of the diagram illustrates how, as a result of this exposure, the material accumulates in the body to an extent dependent upon the solubility of the material deposited in the lung. With materials which are for all practical purposes insoluble, the amount accumulated in the body increases steadily at a constant rate proportional to the atmospheric concentration. The material remains in the lungs more or less permanently, even after exposure ceases. With materials which are removed from the lungs by solution and are eventually excreted, or removed and eventually eliminated in some other way, the amount accumulated in the lungs, tissues, and skeleton rises to a maximum level depending upon the atmospheric concentration and the properties of the material. It should be pointed out here that once this state of equilibrium is attained the amount accumulated in the body is independent of the duration of exposure and if the effects on the men are non-progressive the risk to health is a function of the atmospheric concentration alone and the duration of exposure may safely be ignored.

There is, then, a continuous spectrum of different kinds of risk from inhalation, varying from those in which the amount of the material in the body is the result of the accumulated exposure of a life time to those in which it is the result of exposure for a few minutes only.

Variable Concentrations

When the atmospheric concentration of the material is constant or very nearly constant the evaluation of the risk is fairly straightforward. There can, however, be few industries in which this situation holds. The importance of a given atmospheric concentration of harmful material depends on its magnitude and its duration. Some knowledge of the variability of concentration with time is thus essential for a proper appraisal of the risk to health. Further, from the frequency and magnitude of the variations it is possible to estimate the risk of a dangerous situation arising in the future.

The ventilation of factories and workshops may depend very much on weather conditions. Even in places such as coal mines, where the ventilation current is rigidly controlled, the operations which give rise to air pollution are so numerous and variable that large fluctuations in concentration occur. The importance of these fluctuations of concentration depends upon the position of the harmful material on the scale of accumulation-time. If the amount of material in the body depends upon a lifetime of exposure short-term fluctuations of concentrations are of no importance except in so far as they render the average level of concentration difficult to determine. This will be the case with the pneumoconioses, in which the rate of accumulation is proportional to the average concentration. A progressive accumulation of the material occurs under exposure to even the lowest concentrations. On the other hand, in the case of the toxic gases or any material which is excreted, exhaled, or removed in some other way, the body can tolerate indefinitely atmospheric concentrations materially higher than those found in clean air. When equilibrium is reached the material is being eliminated from the body as fast as it is being deposited in the lung. However, short-period, high concentrations may lead to a temporary accumulation in the body sufficiently great to be harmful. For example, it is generally accepted that an average concentration of carbon monoxide of 100 parts per million for a 40-hour week is quite safe, although were the same dose inhaled in one hour, that is with a concentration of 4,000 parts per million, then almost certainly the exposure would be fatal (Henderson, Haggard, Teague, Prince, and Wunderlich, 1921). Thus in this case the fluctuations of concentration from hour to hour are of primary importance.

These considerations have an important bearing on the sampling period of instruments used to measure concentration. In the case of coalworkers' pneumoconiosis an instrument which sampled for as long as a week would be adequate to detect a potentially dangerous environment. On the other hand, in the case of the toxic gases an instrument which integrates the exposure over a week will fail to detect fluctuations in concentration which nevertheless are of sufficient duration to give rise to serious effects on the workers. An instrument which samples for an hour or even less might then be required to detect these small-period fluctuations. In other words, the period covered by each sample should be determined from a knowledge of the period of accumulation required to produce a harmful effect on man, as well as from a knowledge of the magnitude of the fluctuations in concentration.

The Habits of the Workers

To assess the risk to health from studies of the workers' environment it is necessary to measure the period of exposure to the air contaminant. For those materials which accumulate slowly the amount accumulated by the body will be roughly proportional to the time spent at work each day, while for the toxic gases the number of occasions for which the worker is exposed to concentrations above a specific level will again be roughly proportional to the time spent at work. The risk to health in both cases is higher for those workers who work the longest hours.

It might be thought that the period of exposure would vary very little from one group of workers to another in the same industry or from one worker to another, and could thus be assumed constant. We have investigated this assumption in coal-mines. Surveys were made of a particularly important and well defined occupation, that of the coal-getters at a number of collieries. The principal results at four collieries are illustrated in Fig. 2. The coal-getters are men who work

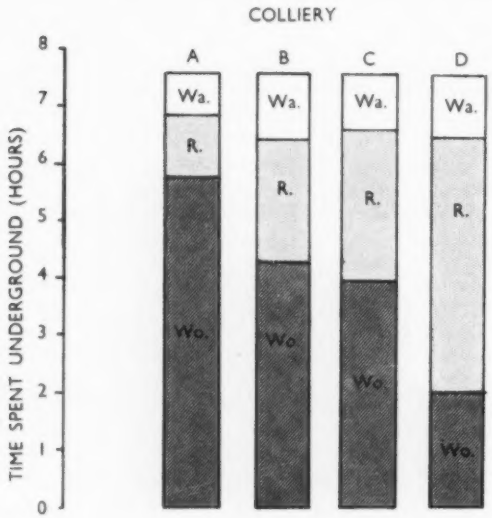

FIG. 2

at the coal-face digging the coal and shovelling it on to a conveyor. Usually it is found that more than 80% of their dust exposure occurs when they are actively engaged on getting the coal or fixing temporary roof supports. Detailed time studies were made at these four collieries to determine the average duration of this period of activity. The four columns in the figure are divided into three parts. The top portion of each column represents the average time spent walking while getting to the coal-face from the pit-bottom at the beginning of the shift and walking back at the end of the shift. The shaded portion is the average time spent actually working at the face, either getting the coal, fixing roof supports or otherwise actively engaged in useful work. The remainder, the dotted portions in the diagram, is the average time spent resting. The mid-shift break for food, lasting from 20 to 100 minutes, is included in this period. It will be seen that the average period of activity varied from five and three-quarters hours at Colliery A to a little under two hours at Colliery D. If the dust concentrations were the same in these collieries these hitherto unsuspected large differences in the duration of the period of activity would indicate that there are large differences in the dose of dust inhaled per day and consequently in the risk of developing pneumoconiosis. Similarly, the total time of exposure to concentrations above a specific level varies in a similar way. This might be of greater importance in other industries.

Individual workers also vary amongst themselves in the time they spend at work each day. Some habitually work overtime while others get through their work as fast as possible. They also vary in the number of days they work each year. It is well known that some workers attend much more often than others. In following the attendance of the coal-getters at one colliery it was found that the number of shifts worked during a year varied from 150 shifts to 300 shifts.

One might argue that these large differences in duration of exposure would not be found in industries other than coal-mining, but in our limited experience of other industries exactly similar conclusions were reached.

Sampling Procedures

It will be clear from the earlier remarks that a really satisfactory sampling procedure must take account of the airborne concentration of the material being investigated, the fluctuations in concentration about the average and the period of time the men are exposed, the relative importance of these factors depending upon the manner in which the material accumulates in the body.

The concentration of air contaminants in a mine or factory varies from place to place according to where the material is produced and dispersed into the atmosphere, and according to the amount and direction of the ventilation. It follows that where air samples are taken at fixed sampling sites, such as the middle of a workshop, subsidiary information is also required to relate these measurements to the exposure of the men not actually working around the sampling instrument. This involves a complicated programme of time studies and surveys to determine the way in which the concentration varies from one position to another.

A sampling procedure which we have found to be much simpler in coal mines and, we believe, would be found equally useful in all other environmental surveys concerned with measuring the risk to health due to airborne contaminants, is that in which the sampling technician directs his attention to an individual worker throughout a working day (Oldham and Roach, 1952). The technician meets the worker when he arrives and samples alongside him until the worker leaves to go home. Samples are taken as far as possible within the workers'

breathing zone. On different days other workers are chosen for study. The particular workers studied are chosen at random from the whole population under investigation. The random sample gives a fair cross-section of the workers and the mean of the sample is an unbiased estimate of the mean for the whole population. The results provide unbiased estimates of the mean concentration, the mean duration of exposure, the variations in exposure from worker to worker and thus from place to place, the magnitude of the fluctuations in concentration for the population as a whole, and their variability from place to place and worker to worker.

The results tell not only the risk to workers but also the working places where the greatest exposure arises and thus pinpoint the most important operations where preventive measures would be most effective in reducing the risk.

Interpretation of the Results

Having measured the exposure of the workers, the next problem is to reduce the results to a single figure which relates closely to the resultant risk to health.

There are, however, very few workers who stay in one mine or factory doing the same job in the same place throughout their working lives, and in order, for instance, to make a fair appraisal of the risk of pneumoconiosis, the result of the accumulated experience of a life time, the pattern of behaviour of the workers must be taken into account. The length of time a man stays in the industry and the frequency with which he changes his job both affect his chances of developing pneumoconiosis.

The situation becomes somewhat simpler with materials which are eliminated from the body at such a speed that the amount in the body and resultant risk to health are determined by the exposure over a period short in comparison with the period that a man stays in a particular job.

With exposure to lead, for example, we could reasonably expect a man entering the industry to stay in the same job for at least a year or two, the period of accumulation for lead. Also in estimating the risk to health due to a toxic gas, in which equilibrium between the body and the environment is attained extremely quickly, the duration of employment and the changes of job are of quite minor importance.

It is sometimes assumed that all men react equally to the same exposure so that there is a fixed level of exposure, measured in units appropriate to the properties of the material, above which all men exhibit a given response and below which none do. However, people do differ from one another in their rate of working and consequently in the rate at which they inhale the contaminant. In addition they differ in their ability to tolerate foreign materials. The magnitude of the exposure which causes a specific response, whether it be a slight dizziness or a serious illness resulting in death, will thus vary from man to man according to their variation in individual susceptibility. In addition, both the measurement of exposure and the detection of the response are subject to error, and will have an apparently similar effect since those whose exposure is underestimated will appear to be unduly susceptible while those whose exposure is overestimated will appear to be unusually resistant. The effect of all these variations is to produce a continuous gradation of increasing risk with increasing exposure (Roach, 1953).

We can conclude from this that although preventive measures such as improved ventilation or dust suppression will reduce the risk to health, they are, in practice, unlikely to prevent the occurrence of symptoms of excessive exposure altogether. For a complete safeguard periodic medical examinations are needed also to detect the men who show the effects of excessive exposure either because they are unduly susceptible or have chanced to be exposed to harmful conditions.

Summary

In estimating the risk to health due to atmospheric contaminants by measuring the atmospheric concentration the essential difference between different materials is in the duration of the period of accumulation. Some materials accumulate in the body until their rate of removal equals their rate of deposition in the lungs, when an equilibrium level is reached. Others are not removed at all, so that accumulation continues steadily throughout exposure. The period of accumulation may therefore be one of only a few minutes, or it may be the whole working life. The period of accumulation determines the time scale of those fluctuations in concentration which need be taken into account.

Examples are given to show that in measuring the exposure of workers it is not safe to assume that their duration of exposure is constant and it is recommended that a sampling procedure based upon the exposure of individual workers be used. In gauging the risk to health the likely duration of employment and the changes of job within an industry must be considered, since both affect the risk when the period of accumulation is of many years' duration. Owing to variations in individual susceptibility and errors of measurement there is a continuous gradation of increasing risk with increasing degree of exposure. Consequently, preventive measures may not eliminate the risks altogether, and periodic medical examinations are needed as well to protect the occasional case of excessive exposure.

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The Problem of Chemical Toxicity

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I shall deal with two aspects only: first, a brief survey of the definition and duties of the chemist, and secondly, a description of some of the ways in which he can help to solve problems of environmental toxicology.

Chemistry and Chemists

Environmental studies in a chemical industry or occupation are made too often *after* an accident has occurred. The action taken usually clears up the bad housekeeping. But the trouble is often due basically to a lack of knowledge of the offending substance. Why is this reverse method of attacking the problem the rule rather than the exception? This question cannot be fully answered but it may be seen more clearly if we consider a few facts about chemistry and the modern chemist. Because chemistry includes the study of substances that occur in living matter it can be said that the chemist is bound ethically to take an interest in their animate as well as in their inanimate functions and locations. In other words he is potentially well suited to investigate the effects of natural and unnatural chemicals on man's health. All this makes an excellent start in solving problems of environmental toxicology. Unfortunately the ideal application of this thesis is often offset by other factors. One of these is the regrettable and modern tendency for chemists and other scientists to overspecialize too early.

A full study in environmental toxicology requires a good knowledge of the "primary" disciplines of chemistry, physics, engineering, and medicine. It also requires the "secondary" related disciplines of biochemistry, biophysics, physiology, biology, and statistics. It may be possible to call in experts to deal with the second group, but it is an advantage if those who are working constantly on toxicological problems have some knowledge of and even a proficiency in these "secondary" subjects. At least one result of this is that it will assist members of the team in talking the same scientific language and will therefore facilitate the progress of research.

There are very few workers in the field of environmental toxicology, and in consequence there are enormous gaps in our knowledge of pure and applied information. This is most serious. Our national chemical industry is great and is expanding, but we are still far behind in our attacks on its special health hazards. I am not criticizing the chemists or scientists but the system of education that has given rise to this state of affairs.

There is no doubt that the chemist who submits himself, partially if not wholly to other disciplines, will achieve a great personal satisfaction in a much wider appreciation of any problem of environmental toxicology that he is called upon to investigate; and, more important, by his now balanced knowledge he will be able to take his place as a valuable member of the team of experts whose duties and obligations have been defined so fully and so forcefully by the President.

Problems in Chemical Toxicity and Methods of Attack

Two extreme forms of toxicity are generally recognized, the acute and the chronic. Although cases of acute poisoning occur with considerable frequency, the overall health of the worker is bound up with his prolonged existence in an environment where he is absorbing continuously low but fluctuating concentrations of a poison.

I shall consider a few of a host of chemicals, other than the hard silica type dusts, that are encountered at work. These are all much more soluble than silica in water and therefore add additional problems of intimate systemic poisoning.

There are three methods by which the chemist can help to unravel problems of industrial toxicology. They are atmosphere sampling, determination of blood levels and elimination rates of the toxic substance, and animal experiments. This is the order in which a study is made today on a substance in current use, and about which little is known. If a new substance is under consideration the order should be reversed.

The first method, namely, atmosphere sampling and correlation of the results with blood levels and elimination rates of the poison, is the best known and probably the most important. A man suffering from chronic poisoning represents the summation of many exposures under varying conditions. In the past too much reliance has been placed on a few "grab" samples. If a scientifically sound evaluation is to be made of a man's environment it is essential to obtain as much information as possible on all aspects of atmosphere contamination. A few grab samples taken *after* a man has succumbed cannot be used to determine accurately past conditions of his exposure or to define tolerable limits of the poison. Much more "pre-accident" information is necessary in order to determine these values and this is notoriously difficult to obtain. There is no doubt that the combination of the lack of specially qualified scientists with the need for employing cumbersome and time-consuming techniques has accounted for the inadequacy of many past surveys.

There are two general techniques for sampling atmospheres. The first is to obtain mass concentration values over a good length of time, e.g. one day or one working shift, and to repeat this as often as possible.

The second technique, which is a development of the first, is to employ a constant recording device. It gives a continuous picture of changing concentrations, and is quite invaluable in detecting specific danger points or careless workmanship. The mercury vapour detector is an example. The use of this instrument is illustrated in Fig. 1. This shows five-minute variations of mercury vapour concentrations in a workshop where metallic mercury was used. The rapid fall at the lunch and tea breaks are very noticeable. Obviously these essential

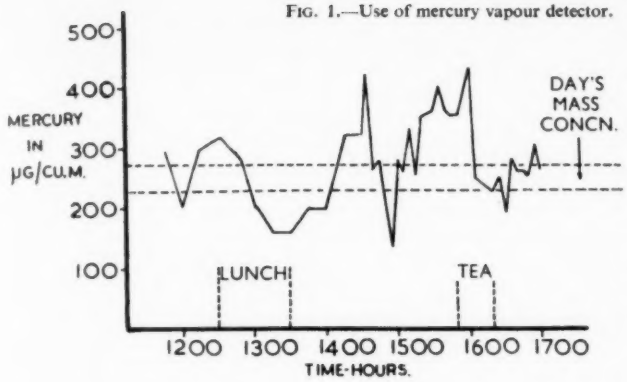


FIG. 1.—Use of mercury vapour detector.

details are not given by determining the average mass concentration figures which were about 250 µg./cu.m. This is an excellent illustration of a constant monitoring device. Its chief advantages are that it can be manipulated easily, that it does not involve the continuous use of complex chemical techniques, and that it analyses mass concentration values into valuable component details.

The correlation of atmosphere concentrations of mercury with symptoms is illustrated and described in a study of "Chronic Mercury Poisoning in Men Repairing D.C. Meters" (Bidstrup, Bonnell, Harvey, and Locket, 1951), and shows that the workshops with the highest atmosphere concentrations of mercury (>100 µg./cu.m.) are those in which the greatest number of cases are found. These also excreted most mercury in the urine (>300 µg. in 24 hours).

The second method, determination of blood levels, urine levels, and elimination rates of the poison, gives indications of the minimum amount of toxic substances in the body. Such routine determinations are also valuable checks that can be used for monitoring workers. For example, periodical estimations of the concentrations of 4 : 6 dinitro-*o*-cresol (DNOC—weedkiller) were made on the blood of spray operators to determine whether they had absorbed dangerous amounts and should be removed from exposure (Bidstrup, Bonnell, and Harvey, 1952). To find the elimination rate of a toxic substance it may be necessary to remove a man from exposure to it for a period of time in order to determine its blood and urine levels. The information gained may make it possible to forecast within reason when he, and therefore, others, may be free from it. This information may also be correlated with diminishing symptoms. An illustration of the use of the elimination rate is given in some studies on the absorption and excretion of DNOC by man.

Preliminary experiments on human volunteers (Harvey, Bidstrup, and Bonnell, 1951) revealed that it would take up to six weeks for a large dose of DNOC to be cleared from the blood. This was confirmed by studying two or three hospital cases. In all it was found that the decay of DNOC from the blood was exponential, that is, the log dose/time relation was linear.

Fig. 2 shows the simple arithmetical plot of dose against time at the top, and the exponential plot at the bottom. There is no doubt that the logarithmic method of treating the results is more impressive than the first. It is probably the most useful because it lends itself to simple mathematical treatment such as the derivation of the half-times of elimination. Although a large number of organic and inorganic substances, natural and unnatural, are excreted in an exponential manner, some metals such as lead are firmly bound to tissues, e.g. bone, and their elimination from the system is less easy to follow. On the other hand there is some evidence that mercury is excreted exponentially (own studies: Grossman, Weston, Lehman, Halperin, Ullmann, and Leiter, 1951). The elimination of some of the common toxic

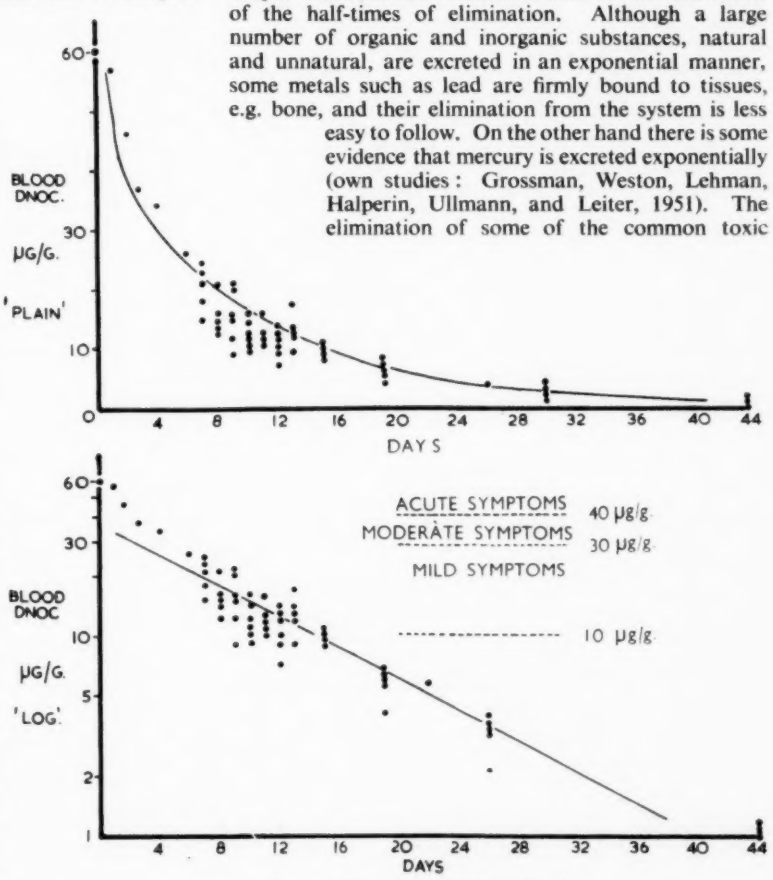
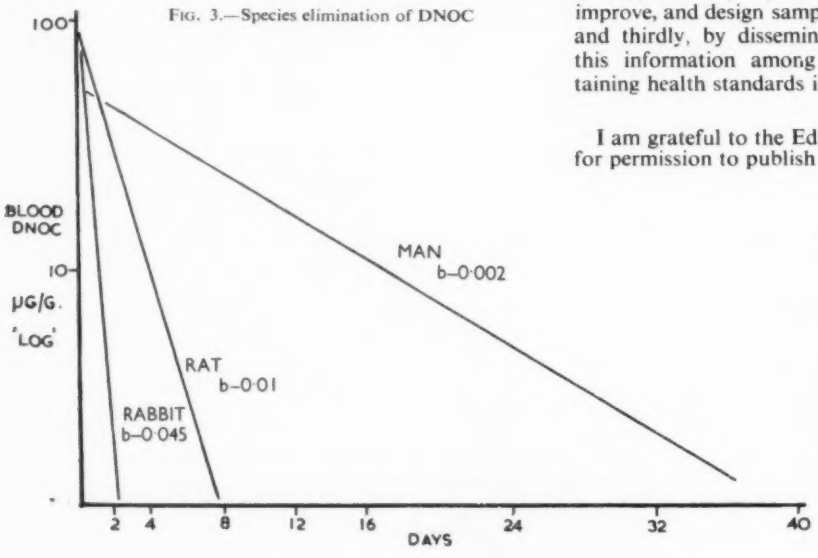


FIG. 2.—Decay of DNOC from blood.

gases such as HCl, Cl_2, SO_2, NH_3 is more difficult to follow since they often lose their identity in the buffer systems of the blood and tissue fluids.

One of the main things the chemist has to determine is whether repeated small doses of a poison will accumulate. If the blood levels of the substance increase, accumulation must have occurred. It will not be possible to apply the results of animal experiments quantitatively to man but it will be possible to demonstrate some of the qualitative effects of the substance. It must be remembered that many pitfalls exist for the unwary in conducting animal experiments. Not the least of these are the quantitative biochemical differences in the various species. This is particularly noticeable in their abilities to deal with unwanted or toxic materials. In support of this I quote a biochemical example clearly expressed by Baldwin (1948) on the evolutionary breakdown of uric acid by different species : " It is interesting to notice that, with the evolution of the more complicated forms of life the tendency as far as purine metabolism is concerned has been to lose old enzymes rather than acquire new ones ". Although uric acid is not a deadly poison and is far removed chemically and physiologically from, say, DNOC or some of the modern pesticides, Baldwin's example illustrates a gradual evolutionary slackening of enzyme activity culminating in man. Man is notably inefficient in detoxicating poisons, and this may well be the result of a reduction in those enzyme systems more specifically concerned with the change or destruction of toxic groups. Bearing these points in mind the chemist should have little difficulty in making a guarded but useful statement about the qualitative toxic nature of the substance. Some of these points are illustrated in Fig. 3 by the studies of King and Harvey (1953) on the comparative elimination rates of DNOC by the rat, the rabbit, and man. Two general observations can be made from the results. First, that man possesses relatively inefficient systems for detoxicating this type of poison, and secondly the need for careful interpretation of animal experiments. In practical terms the curves can be summarized as follows. When DNOC intoxication is present in the three species and is represented by initial blood levels of 60 to 80 μg./g., the concentrations will be reduced to insignificant amounts in two days in the rabbit, eight days in the rat, and 40 days in man. A significant if not wholly unexpected example of comparative toxicology !

FIG. 3.—Species elimination of DNOC



Finally, the chemist must attempt always to improve methods of analysis and sampling. In this the physicist will give him invaluable assistance. The most important line he can take is to develop constant recording devices for the measurement of toxic materials in the atmosphere. I have already quoted the mercury vapour detector as an example of this, and it is possible that the emission spectrograph can be used in a similar manner for some metal dusts.

The Future

If more of us who are chemists are prepared to work in this field and are willing to submit ourselves to related disciplines, some progress will be made, and I have no doubt that this applies to the other members of small investigating teams.

To gain more " external " workers will be difficult, but those inside the industry or occupation itself should also be a source of help. It is wrong that much of the routine work involved in solving toxicological problems should remain for ever the burden of a few specialist " external " teams. I hope that one day we may gain much of our basic information from the " internal " staffs of the industry or occupation. This can be achieved only by three essential developments. First, by the proper realization of the chemist's duties and responsibilities, secondly by an all-out effort to re-examine, improve, and design sampling and analytical techniques, and thirdly, by disseminating the practical aspects of this information among those responsible for maintaining health standards in industry and occupation.

I am grateful to the Editor of *The Biochemical Journal* for permission to publish Fig. 3 in a modified form.

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Occupational Hygiene and the Industrial Designer

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I do not propose to consider the problems presented by unsatisfactory conditions in existing factories and shall confine my remarks to the consideration of hygiene requirements when new manufacturing processes are developed and when the resulting production plants or factories are designed.

Industrial capital investment in this country is now at a very high rate (more than £1,000 million per year), the range of products is expanding rapidly, and the manufacturing processes involved are increasing in complexity. The resulting problems for the industrial designer are correspondingly great in number and complexity. The potential savings in capital and production cost to be derived from good design are very considerable and it is of the greatest importance that industry's development and design procedures shall be such as to yield the best possible results.

Stages in the Design of a New Plant

The creation of a new plant or factory makes a certain pattern; the principal stages are nine, and at certain of these the pattern must be closely integrated with the requirements of occupational hygiene. The nine stages are as follows:—

(1) Fundamental research in the fields of physics, biology, and chemistry, leading to the discovery of a new product and to determining the appropriate process for manufacturing it; (2) applied research principally in the fields of mechanical, electrical, and chemical engineering and of metallurgy, leading to the evolution of methods of implementing the selected production process; (3) process development and experimental work involving the design, building, and operation of semi-technical and pilot plants; (4) preparing the technical flowsheets and specifications of requirements for the final production plant or factory; (5) preparing engineering flowsheets based on the technical flowsheets; (6) scheme layout design work covering buildings, plant, roads, railways, etc; (7) selection or design of items of plant equipment; (8) detailed design and layout; (9) preparing final drawings for shop fabrication and for construction or erection on the site.

The requirements of hygiene demand attention to a greater or lesser degree at all these nine stages and contact with those who are to be responsible for the health and safety of the work people at the research stage is most important. There will be cases in which the difficulties introduced by the use of a particular process may necessitate an alternative mechanical method or chemical route, or additional medical investigations may be necessary before a plant can be designed with confidence.

If the designer is to have a clear understanding of all requirements before he embarks on developing his design, it is very necessary that hygiene requirements first studied in stages (1) and (3) should be fully stated at stage (4) and specified as an adjunct of the technical flowsheet. This specification must make known to the designer details of any health hazards associated with the various substances and operations employed in the process: it must, for example, inform him of the permissible concentration of a toxic gas in the atmosphere of a building so that he can determine what type of gland he must employ for process fans in the plant or whether the fans must be placed outside the building or perhaps in a cubicle. He must know if special washing facilities are required for workers handling a particular substance or whether the dust from the grinding of some material introduces a danger of pulmonary disease thus requiring special extraction equipment.

At the technical and engineering flowsheet stages it is not sufficient to examine matters only from the point of view of hygienic conditions in relation to operation; the maintenance aspect must also be closely considered since in many cases, for example, where radio-active compounds are handled, the hazards to health associated with maintenance may be such that either no maintenance is possible or replacement of consumable elements may have to be effected by remote control servo mechanisms.

In the later stages of design, particularly at stages (6) and (7), it is most important that the hygiene specialists should be in very close touch with the work of design and layout and they should critically examine what is proposed by the designer. The table on page 62, although not complete, emphasizes the necessity for close attention to hygiene requirements in the design of each element which makes up a complete plant or factory. In it I have set out factors under three main subject headings—environment, occupation, and amenities, but several of them apply to all three subjects.

The design problems associated with the factors in the table do not in themselves present any great difficulties: the technical issues involved are, with some exceptions, comparatively simple. The real problem is not one of design but of organization and procedures, one of ensuring that all the factors will be properly considered by the proper people at the proper time and that appropriate action will be taken. I suggest that the prerequisites for success are: (1) The availability of basic data and of specialist advice; (2) close and continuing cooperation throughout the design stages of the designer with those responsible for hygiene; (3) a full specification of requirements for satisfactory hygiene conditions; (4) critical examination of all plant design and layout proposals by those responsible for hygiene; (5) definite allocation of responsibility for matters of hygiene; (6) the interest and insistence of higher management in the attainment of healthy working conditions, and a real concern on the part of the whole design team for those who will have to spend their working lives operating and maintaining the plant.

TABLE

DESIGN RELATED TO HYGIENE REQUIREMENTS

Environment		Occupation		Amenities	
Physical	Chemical	Physical	Mental	Health	Welfare
Lighting	Liquids	Effort	Interest	Sanitation	Canteens
Heating	Fumes	Posture	Concentration	Refuse disposal	Rest rooms
Ventilation	Gases	Hazard	Monotony	Washing	Bus shelters
Humidity	Dusts	Temperature	Isolation	Change rooms	Cycle sheds
Colour		Working space		Clothing	Car parks
Noise				Medical services	Playing grounds
Smell					
Dirt					
Floor surface					
Stairways					
Doors					

Basic Data and Specialist Advice

The research workers, the development staff, and the engineering designers cannot be expected to have expert knowledge of hygiene requirements and must, therefore, be provided with information. This can be given by literature, which in suitable form is unfortunately scarce, or by medical officers with a specialist knowledge of occupational hygiene. A combination of both is desirable and to make this possible handbooks on the subject written specially for the industrial designer should be produced.

Cooperation

The achievement of adequate cooperation must not be left solely to the research worker, the development staff, the engineering designers, and others directly concerned with the design work. Adequate cooperation often does arise from the natural interest of all these persons but if it is to be assured in the fields of health, safety, and welfare it must be positively organized by management.

Specification of Requirements

Experience has proved the importance of a comprehensive technical specification from which to develop a manufacturing process, whether the process be a physical or a chemical one. The importance of a hygiene specification is equally great. I recommend very strongly that for all projects the requirements of hygiene should be the subject of a documentary statement prepared during stage (4) of the design.

Examination of Design

Engineering drawings are not easily read or understood by medical officers, labour and welfare officers, and others outside the technical design team. Designers must devote adequate time to explaining their proposals, and I would particularly mention the value of isometric drawings and of models.

Responsibility

Although it would seem that responsibility for matters of hygiene should be placed on a medical officer, I think it would in practice be better placed on the individual who will in due course be responsible for the operation of the plant or factory.

Interest

The physicists, chemists, engineers, metallurgists, and other technical staff in the design team are naturally concerned primarily with their specialist techniques and hygiene is for them in general a secondary matter. An adequate interest in hygiene must be created if success is to be achieved. And this interest and a determination that plants and factories shall be healthy and safe places in which to work must come from higher management.

With all these prerequisites there still remains much in the way of routine procedures which will help to ensure success. I will refer to two procedures which have proved to be of value.

The first is the use of a specially prepared list of all issues which may arise in connexion with hygiene in the design of a plant or factory. This *aide mémoire* can provide an invaluable means for checking at every stage that all aspects have had proper attention.

The second procedure is one of recording that all interests have been consulted at each stage of design and that decisions taken have been implemented. The record provides a detailed history sheet of the project throughout all stages of design.

Working conditions in our factories are being steadily improved but there are still some black spots. These must and will be removed but it is more important still that by using sound design procedures no new black or even grey spots will appear. The provision of healthy, safe, and agreeable conditions for those who work in our factories is a moral obligation. It is also an economic necessity since these conditions, without doubt, play a great part in the achievement of maximum productivity.

BOOK REVIEWS

Annual Report of the Chief Inspector of Factories for the Year 1951. Cmd. 8772. London : H. M. Stationery Office. (6*s.* 6*d.* net.)

The year 1951 marks the half century since the passing of the Factory and Workshop Act of 1901. Since then the Factories Act, 1937, as amended by the 1948 Act, has been the major legislation affecting the health, safety, and welfare of the industrial worker. It is not therefore surprising that in this report the Chief Inspector of Factories should survey the main changes that have taken place over these 50 years.

In most parts of the country there is a choice of industry for the worker beyond his dreams of 50 years ago. In 1951, there were a fifth as many factories without power as in 1901 but twice as many with mechanical power. This has removed from the worker many of the dirty, heavy jobs of the past but has added new hazards.

The steady increase of the number of women employed in factories received extra momentum during the two world wars.

Great advances have been made in standards of cleanliness, lighting and sanitary and washing accommodation in factories, partly by the strengthening of legislation and partly by the changing attitude of employers.

General and particularly local ventilation have brought about great improvements in the atmospheric conditions of work-places by the elimination of high temperatures, removal of dusts and fumes, and the increase in air space per worker.

In the field of accidents and safety both the advances of the mechanical sciences (by which, for example, old methods of providing power have been superseded by individual electric motors) and the considerable strengthening of the law, which now places certain responsibilities on the makers of machinery, have been effective. It is, however, difficult to assess the extent of the improvement since comparable accident statistics are not available.

In the last 50 years personnel management and welfare have shown remarkable advances. Although there were some isolated firms who even 50 years ago were carrying out policies which would today by contemporary standards be regarded as enlightened, it is only in the last 10 or 15 years that there has been a universal change in attitudes of management towards labour.

One of the biggest changes, and perhaps the one with the most revolutionary social consequences, is the number of hours worked per week. In 1901 it was legal and commonplace for women and young persons to work between 55 and 60 hours per week. Today, the 44-hour week is probably as common as the maximum legal 48, and the five-day week is almost universal.

The changes in factory conditions have reflected changes throughout the social conditions in the country, and the difference between the ill-clad, ill-fed, puny factory workers of 1901 and the healthy, well-dressed workers of today is no less striking than the difference between their working environments.

Turning to the report on the current year, 1951, the traditional pattern and form has been followed, but the opening section deals with the various joint committees on which the department is represented and are concerned with safety in a variety of industries or of specific machines.

While the total number of reported non-fatal accidents fell by 5%, there was a rise in the number of fatalities compared with 1950. Comparing accidents with those of 1939, it is disturbing to find how big an increase occurred in those concerned with the use or driving of vehicles. The table which compares the accident rates between 1944 and 1951 is, however, extremely misleading. Although it appears that there were only 25 accidents per 1,000 employees in 1951 compared with 40 in 1944, a drop of 43%, no account is taken of the number of man hours worked in each year. If allowance were made for hours worked the reduction in accident rate would be considerably less impressive.

The important and topical problem of the employment of the elderly receives only indirect attention in an interesting section on accidents. There is inadequate evidence to state whether the over-60s have more than their share of accidents or whether, on the whole, they are relatively less liable to accidents. It is suggested, however, that the skilled workers can carry on their normal work long after the age of 60 and that age does not appear to increase the liability to accident but tends to increase the severity of any injury.

Accidents to young people were rather fewer in 1951 compared with any of the last seven years and, while this may be regarded as satisfactory, it is suggested that there could be further improvements if there were better training of young people. The problem of training is not solely a technical one concerned with accident prevention. The change that takes place when a child leaves school and starts earning his living, whether in factory, shop, or office, is one that imposes considerable stresses and demands much readjustment. The doctor, the nurse, the training officer, the supervisor, and others can all play a part in determining whether this adjustment will be successful. The penalty of failure may be an injury ; it may be the first step in a history of drift or it may be less calamitous.

In discussing health and welfare the Chief Inspector reviews the consequences of three recent codes of regulations, namely the Pottery (Health and Welfare)

Special Regulations, 1950, the Building (Safety, Health, and Welfare) Regulations, 1948, and the Blasting (Castings and Other Articles) Special Regulations, 1949.

In regard to the first two there has been less progress than might have been hoped. Shortage of material and labour is given as one of the reasons; administrative difficulties as another. It is suggested that there comes a time, after the introduction of new regulations, when the art of persuasion must give way to enforcement by prosecution which produces effective change in the behaviour of the defendant firm and is also a great stimulus to others.

The building industry is a dangerous one: there were over 12,000 accidents in the year and 222 fatalities. If these tragedies are to be reduced a more active willingness to comply with regulations is required on the part of employers, and possibly this cannot be achieved without the help of an increased factory inspectorate. Though the authorized staff of the inspectorate is 379, the actual number in 1951 was only 340. It is difficult to believe that even 379 inspectors could ensure the regular and thorough inspection of over 200,000 factories with mechanical power, 2,000 docks, 45,000 building sites, besides the numerous other premises to which some or all of the Factories Acts apply. As the report states, it was not possible to visit every factory or other premises under the Act in the course of the year.

The good firm seeking the advice and help of the factory inspector may consume as much time as the bad one which is only too anxious to avoid his attention. If the inspector is to satisfy the demands made upon his time by these two types of employer, it seems unlikely that he will have any left over for the firm that neither seeks nor avoids him but which could generally profit from a gentle prod or friendly advice.

The factory inspector is also required to conduct legal proceedings; 959 charges were brought against 548 firms and 30 of these prosecutions were dismissed.

The part of the Factories Act that produced the largest number of prosecutions was that dealing with safety. There were 341 charges of which 246 were following death or injury and 95 where no such injury occurred. Illegal employment led to the prosecution of 59 firms. This included the employment of women or young persons at night, on Sunday, or after legal hours.

It is clearly misleading to assess the work of the Department in terms of the number of factories visited in the course of the year. However, the comparative figures are given for 1946 and 1951. They were almost exactly the same although there were fewer inspectors in the latter period.

H. G. MAULE

Surgery of Repair as Applied to Hand Injuries. By B. K. Rank and A. R. Wakefield. (Pp. 256; 188 figures. 40*s*.) Edinburgh: E. & S. Livingstone. 1953.

The admirable studies of Kanavel on infections of the hand greatly clarified our understanding of the anatomy of sepsis and its treatment. They had however the sad effect of concentrating surgical attention and clinical teaching on the ravages of infection while neglecting the more important sphere of repair to the traumatized hand. In recent years the zeal and enthusiasm of Bunnell and Koch have done much to reorientate our ideas and techniques. It has, however, in the past been difficult to obtain adequate information of the more advanced practice in the surgery of hand repair without a pilgrimage to the occasional specialized centre, and it is opportune that two distinguished Australian surgeons, Rank and Wakefield, have published their excellent book. This deals with the practical aspects of primary treatment to the soft and hard tissues, the treatment of the unhealed wound, the "frozen" hand, and the management of the established scar deformities and burns. Preventive and organizational aspects are also covered with appropriate emphasis.

This monograph is the fruit of their personal experience and contrasts delightfully with the "scissors and paste" school of surgical literature. Although both authors are plastic surgeons they have carefully avoided overstressing elaborate plastic techniques and have kept a sound and discriminating balance throughout.

The text and illustrations are excellently printed, and, although there are several minor misprints, the year of one paper being quoted as 1915 instead of 1951, the whole volume can be heartily recommended to any one concerned in the prevention or treatment of the injured hand. It is far and away the best book of its kind and should be made compulsory reading for every casualty officer and practising surgeon.

R. P. JEPSON

Fundamentals of Clinical Orthopedics, Vol. 1. By Peter A. Casagrande and Harold M. Frost, Jnr. (Pp. 582; 390 figures, $18.50.) New York: Grune & Stratton. 1953.

There is little which is new or controversial in this book, which endeavours to cover the whole of orthopaedic surgery, including fractures. There is, in addition, a brief account of some of the anatomy, physiology, and pathology concerned. Herein lies its main defect. In order to include such a broad view of the subject detail has been sacrificed and much of the text consists of very brief summaries.

The established or trainee orthopaedic surgeon looking for guidance on difficult problems will not, on the whole, find the answer here.

The book, however, is entitled "Fundamentals" and as such it will provide a valuable source of information for the undergraduate student and those seeking the broad outlines of the subject.

C. G. ATTENBOROUGH

Oral Manifestations of Occupational Origin. An Annotated Bibliography by Various Authors. (Pp. 41; 20 cents.) Federal Security Agency, Public Health Service, Division of Occupational Health, Washington 25, D.C. 1952.

This is a very useful bibliography of 138 references. It is well worth a place on the shelf of any doctor working, in particular, in a chemical industry. It deals with the

effect on the mouth and its contents of acids, bacteria, dusts and gases, inorganic substances, metals and organic compounds, and physical factors such as foreign bodies and ionizing radiation, and pressure changes. There is also a section on cancer of the mouth, and the bibliography concludes with a general review and an index of authors.

One of the striking things is that it is almost entirely composed of descriptions of the clinical effects of environmental abnormalities with little or no information of their time-concentration relations. This is not a criticism of the bibliography, but rather of the orientation of present-day work. There are one or two places in it where the balance is a little uneven , for instance, about 250 words are taken up in describing a single case of the rare condition of blastomycosis of the oral cavity.

R. C. BROWNE

Medicine. Vols. I and II. Edited by Hugh G. Garland and William Phillips, with Foreword by F. A. E. Crew. (Pp. XX + 2146 ; illustrated. £6.) London : Macmillan. 1953.

The appearance of a new textbook of medicine by 42 British authors is an important event in medical education in this country. To have undertaken the vast labour involved in its production the editors must have felt that existing textbooks were failing to meet a modern need of medical students. More than 500 out of the book's 2,000 pages deal with the concepts of health and disease, the social, psychological, nutritional, and genetic origins of disease, its natural history, and the principles of its diagnosis and treatment and rehabilitation. It thus reflects the good physician's realization that he is concerned with people and not with diseased organs, and that this concern must extend to the inheritance, mind, personality, home, and work of his patient and the part that these influences play in his patient's complaints. A chapter on vital statistics introduces the student to the necessity for looking outside the clinic to see the relative importance of different diseases, and to appreciate the discipline of the statistician's assessment of his contribution to longevity.

There is no doubt that these sections of the book provide something that the student needs badly and cannot readily find in any other general text. Whether the overburdened and harassed student will have the patience to derive full benefit from these chapters is another question. They are long, and there is considerable overlapping, not only between each other but also with other parts of the book. With such overlapping there is inevitably some conflict of opinion. For instance, in the section on " Psychosomatic Medicine " Wittkower and O'Neill emphasize that gastric and duodenal ulcers are separate clinical entities, but they are treated as one by Jennings and Bomford under " Diseases of the Digestive System ". Perhaps a discussion of the confusion that the student so often feels as he encounters divergence of views among his teachers might have been helpful. The question of observer error is not mentioned. Methods of clinical examination and their results are described in orthodox fashion with little or no reference to their unreliability.

The greater part of the book is devoted to a thorough and systematic account of diseases of the various systems, including psychiatric disorders, written for the most part on orthodox lines, with a notable exception in the stimulating section on " Diseases of the Digestive System ", whose tone is set by the opening phrase, " The gut has a problem to solve ". The reader is left in no doubt of the validity of this statement and that the doctor, too, has problems to solve. The general level of description and discussion throughout appears to be aimed at undergraduates, and yet the text is rather more detailed than the majority will need without giving sufficient detail or references to satisfy the postgraduate ; 15 pages are devoted to electroencephalography—scarcely required by the undergraduate. Perhaps this is the most serious criticism of the whole work. It could be shortened and at the same time improved by more references to guide the more inquisitive reader to the original evidence for many inevitably dogmatic statements, and to fuller accounts of rarer diseases than even a book of this size can provide. Some chapters do provide references, but many omit them altogether.

The industrial medical officer will be pleased to find industrial diseases considered in four separate sections. There is a long chapter on " The Skin in General Medicine " by J. T. Ingram, which includes a useful if short account of industrial dermatology with special reference to problems arising from the award of industrial injury benefit. There is a valuable account of aviation medicine by K. G. Bergin, including both accounts of physiological and clinical problems. A. J. Amor contributes one chapter on " Diseases Principally Encountered in Industry " and another on " Industrial Diseases of the Lung ". The first of these, 28 pages in length, provides a useful summary of the provisions of the Industrial Injuries Act with lists of prescribed and notifiable diseases. The incidence of industrial diseases is discussed in the light of 1946 figures. After an account of the chief means of access of noxious substances to the body, and their physicial nature, short accounts are given of the effects of the commoner industrial poisons, but there is no mention of treatment. The second of these sections, 25 pages in length, emphasizes the great importance of the pneumoconioses especially among coal miners. Not everyone will agree with the account of the pathogenesis of these diseases since it includes views such as that " coal actually increases the fibrogenic action of quartz " whereas all it has been shown to do in experiments is to delay the removal of small quantities of quartz from the lungs. These sections on industrial disease will be useful in attracting the attention of the clinical student to an often neglected subject, but will not help the postgraduate seeking detailed or modern information.

On first opening this book the reader is encouraged by the vigorous and enlightened atmosphere of the opening chapters ; it is thus all the sadder that, with honourable exceptions, many of the systemic chapters are cumber-

some, often inaccurate and devoted wholly to the clinical and therapeutic, rather than the preventive, approach to medicine. Perhaps in later editions the heavy burden of the later chapters may be lightened. The two volumes might then consist on the one hand of the principles and background of medicine and on the other of the details of nosology. Many doctors at all stages of their careers might then enjoy the wisdom of the former without necessarily having to concern themselves with the latter, for which they may want to turn to more advanced works. The price of the book as it stands may deter many students from deriving the great benefit that it offers. If the first part were separately published it would surely find a place at many medical bedsides for the leisurely reading and digestion that it requires. The editors are to be congratulated on their enterprise and one hopes that in the later editions, for which there will no doubt be a demand, the redundances and inaccuracies may be corrected, so that this textbook may be made throughout as worthy a contribution to the literature of medicine as the editors and their contributors have so nearly made it.

C. M. FLETCHER

Report on the Health of the Army 1949–50. (Pp. 137). Published by the War Office. 1953.

Perhaps the most fascinating aspect of this interesting report is the changing character and role of the British soldier since the turn of the century. On the average the soldier at the start of the century could expect to be admitted to hospital with venereal disease at least once during his service with the colours, and probably with malaria and an injury as well. The enteric fever rate was ten times what his modern counterpart would expect and 50 years ago he would be about as likely to be in hospital with alcoholism as with tuberculosis. Part of the differences are explicable in the change of character which has taken place in 50 years, but part undoubtedly is a mere matter of change in terminology (or treatment) of a disability. The modern soldier is about ten times as likely to be invalided out on psychiatric grounds; probably his Boer War counterpart was similarly discharged simply as a bad soldier. There is evidence, too, of a demand for physical fitness of a much higher standard than formerly and recently intelligence tests have been introduced to make sure that the less intelligent are excluded. The soldier of 1950 must not only be physically fit to bear arms, he must be mentally fit as well to understand the modern weapons of war. This has increased the status of the soldier and must ultimately exert a beneficial effect on recruitment.

The army has been quick to learn that fitness, welfare, and efficiency go hand in hand, and it is fair to say that British military hygiene has been, for years, an example to armies throughout the world. An increasing amount of research is being undertaken by civilian and Army teams into environmental hygiene from subjects as diverse as mosquito-proof clothing to fluorine in water supplies. With the increase in mechanization and machinery, the army has more workshops and is increasingly exposed to the special hazards of industry. Meetings were held of the Joint Services and the Factory Department Committee on Occupational Health, and it is interesting to note that the Army is now directly interested in toxicology.

The section on statistics is most instructive and the statisticians must be praised for retaining the breakdown of previous reports rather than succumbing to the temptation of making a new arrangement. Taken as a whole, skin disease (not including venereal disease) is far the greatest waste of man-power both in the number of cases and in the loss of time during treatment. This is especially true of the Far East Land Forces with a high incidence of fungus infection, but disease due to the pyogenic bacteria is common in the Middle East and not uncommon in the army at home; the United Kingdom, however, has a higher incidence of the seborrheic and eczematous types. In all theatres either skin disease or injury constitutes the greatest single loss of man-power followed by respiratory disease, tuberculosis, tonsillitis, and peptic ulcer in the United Kingdom. The high incidence of otitis media and externa in all theatres is worthy of note and it is gratifying to follow the continued fall of all those conditions which we know how, at least in some measure, to prevent. The malaria figures, thanks to paludrin, which seems to belong more to preventive than therapeutic medicine, are very small.

J. P. W. HUGHES

Fourth Report of the Ministry of National Insurance for the Year 1952. (Pp. 102; 3*s.* 6*d.*) London: H. M. Stationery Office. 1953.

The Report gives some idea of the size of the job which the Ministry of National Insurance carries out. It is responsible for the distribution of some £480 million each year in insurance benefits and family allowances, and for receiving and accounting for some £450 million in insurance contributions. The amount of work entailed is indeed colossal; for instance, some 26 milllon ledger accounts are maintained, and nearly 10 million claims are dealt with each year. During the particular year under review an increase of benefits was sanctioned by Parliament; this broadly restored the purchasing power of the main National Insurance benefits to the 1948 level.

Sickness.—New claims for sickness averaged 127,000 a week during 1952, a lower figure than for any of the three preceding years, for which the overall average was 139,000 per week.

For the first time the Report gives figures, analysed according to diagnosis of medical certificates received in support of claims to sick benefit, for the year 1950. Attention is drawn to their limitations, and research workers wishing to use them are advised to consult the Statistical Division of the Ministry before doing so. The Report contains two interesting tables in which a summary of this information is given. Bearing in mind that there are two and a half times as many men as women insured, the excess of certificates from women suffering from psychoneurosis and anaemia, and the

excess for men suffering from peptic ulceration is strikingly brought out in the tables. The hope is expressed that further analyses of sickness experienced in the insured population will be possible. It is to be hoped that age will be taken into account in this extended work.

Retirement Pensions.—Nearly three-quarters of the total expenditure on all National Insurance benefits during the year ending March 31, 1952, was devoted to retirement pensions which took 275 million pounds. It is estimated that 25 years hence this figure will have grown to nearly £700 million. Earlier reports have included analyses of samples of persons reaching pensionable age, but in view of the importance of the subject it has been decided to undertake a full enquiry to discover the importance of various factors influencing people in their decisions to retire or continue at work. For instance, it is not known how far deficient health and lack of opportunity of suitable employment contribute to this decision. Similarly the effect of superannuation schemes and the practices of employers and trade unions are influences the importance of which had not so far been assessed.

Injury Benefit.—The total number of claims for injury benefit in 1952, the rate for which was raised from 45s. to 55s. a week in July, was 775,000, a slight increase over the number in 1951, but still below the figure for the two previous years.

The great majority came from the heavy industries, and coal-mining again accounted for more than one-third. About 5% of insured men and 1% of insured women received injury benefit in the course of the year, the average periods being about four and five weeks respectively. Industrial injury benefit cost over £8½ million for the year ended March 31, 1952.

The experience in the working of the Regulations under which nurses and certain health workers are insured against tuberculosis shows that almost 800 such claims are successful each year.

Disablement Benefit.—The Report indicates trends in the development of disablement benefit (which in 1952 cost £7 million). The number of claims for disablement benefit has risen each year and was 96,000 in 1952, as compared with 86,000 in 1951. Nevertheless, disablement benefit is only claimed by a small minority of injured people. In 1952, the claims for disablement benefit were only just over 12% of the claims for injury benefit.

The number of disablement pensions rose by 19,000, or one-third during 1951 so that 76,000 disablement pensions were being paid at the end of the year. Of these three-quarters were for accidents and one-quarter for prescribed diseases. At the end of 1951, nearly 40% of the disablement pensions, including those for pneumoconiosis, were being paid to colliery workers who represent less than 5% of the insured population. About 10% were being paid to women, who are normally employed in the lighter industries. Nearly two-thirds of the pensions were for disablement of 20 or 30% and only about one-quarter for more severe disablement. Less than 4% of the pensions were at the 100% rate. Those still 100% disabled by industrial accidents after two or three years represent less than one in 2,000 of the people who claim injury benefit for accidents at work.

Finance.—The Report deals at some length with finance and contains a statement by the Government Actuary. Each year there has been an excess of income over expenditure but this is now changing. Additional expenditure resulting from higher rates of pensions and other benefits and the steadily increasing number of people who will become eligible for these are the cause of this change. Expenditure will begin to outstrip income by 1954/55, and in 25 years the deficiency to be met by the Exchequer each year is likely to be in the region of £417 million. The Government Actuary points out that this is not a new feature but is an inescapable result of granting full pension rates to contributors of all ages and to existing pensioners, even though they have not paid the requisite contributions and of the method of finance adopted by the State to meet the huge liability thus created.

The Industrial Injury Fund is not likely to become a burden in this way. Excess of receipts over payment amounted to £19 million during the year and the balance in the fund on March 31, 1952, was £78 million. The Report emphasizes, however, that this balance is essential at this stage if the fund is to remain self-supporting in the future since the annual expenditure on disablement pensions will increase automatically for many years.

This report is full of interesting information and should be widely read by medical men in industry.

R. E. LANE

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Vorbeugende Gesundheitsfürsorge. By W. Hagen. (Pp. 131. DM. 7.20.) Stuttgart : Georg Thieme Verlag. 1953.

Physical Medicine and Rehabilitation. Edited by Basil Kiernander, with Introduction by The Rt. Hon. Lord Horder. (Pp. 610 ; illustrated. 63*s*.) Oxford : Blackwell Scientific Publications. 1953.

Die entschädegungsflichtigen Berufskrankheiten. By M. Bauer. (Pp. xii + 176. DM. 9.60.) Stuttgart : Georg Thieme Verlag. 1953.

Lesioni del Cristallino da Radiazioni industriali. By Felice Redaelli. (Pp. 40. Lira 320.) Libero docente di patologia oculare e clinica oculistica, University of Milan.

Risiko und Kosten in der Krankenflegeversicherung. By Alfred J. Hosch. (Pp. 127. Sw. frs. 12.) Berne : A. Francke AG. Verlag. 1953.

Zur Genese des Diabetes mellitus und des Bronchialasthmas. By M. Bauer, with Foreword by Cl. Dierkes. (Pp. 113 ; illustrated DM. 9.60.) Stuttgart : Georg Thieme Verlag. 1953.

Rudolf Virchow. By Erwin H. Ackerknecht. (Pp. 304 ; illustrated. $5.00.) The University of Wisconsin Press. 1953.

Symposium on Fatigue. Edited by W. F. Floyd and A. T. Welford. (Pp. viii + 196 ; 47 plates. 24*s*.) London : H. K. Lewis. 1953.

Sécurité et Hygiène du Travail dans la Verrerie à la Main. (Pp. 144 ; 50 figures. Fr. frs. 200.–.) Paris : Institut National de Sécurité. 1953.

Leistungssteigerung—Leistung, Übermüdung, Gesunderhaltung. By M. Hochrein and I. Schleicher. (Pp. 283 ; 53 figures. DM. 27.–.) Stuttgart : Georg Thieme Verlag. 1953.

Leibesübungen mit Körperbeschädigten, Vol. II. By Hans Lorenzen. (Pp. 249 ; 227 figures. DM. 22.50.) Stuttgart : Georg Thieme Verlag. 1953.

Toxic Solvents. By Ethel Browning. (Pp. 168. 18*s*.) London : Edward Arnold. 1953.

Pneumoconiosis Abstracts, Vol. I, 1926–1938. (Pp. xi + 347 ; illustrated. 63*s*.) London : Sir Isaac Pitman. 1953.

Strahlenschutz und Sonstiger Arbeitsschutz bei der medizinischen Anwendung von Röntgenstrahlen. By Wilhelm Ernst. (Pp. 97 ; 22 figures. DM. 7.80.) Stuttgart : Georg Thieme Verlag. 1953.

Verhandlung der Deutschen Gesellschaft für Arbeitsschutz, Vol. I. By Edwart Mager. (Pp. 146 ; 36 figures. DM. 20.–.) Darmstadt : Verlag von Dr. Dietrich Steinkopff. 1953.

Outlines of Industrial Medicine, Legislation, and Hygiene, 2nd ed. By James Burnet. (Pp. 122. 10*s*. 6*d*.) Bristol : John Wright ; London : Simpkin Marshall. 1953.

THE OCTOBER (1953) ISSUE

The October (1953) issue contains the following papers :—

Dust Sampling in the Control of Coal Miners' Pneumoconiosis.

A Method of Relating the Incidence of Pneumoconiosis to Airborne Dust Exposure. By S. A. Roach.

The Nature of the Variability of Dust Concentrations at the Coal Face. By P. D. Oldham.

The Importance of the Time Factor in the Measurement of Dust Exposure. By B. M. Wright.

Airborne Dust in Coal Mines : The Sampling Problem. By W. M. Long.

Mortality in Relation to the Physical Activity of Work. A Preliminary Note on Experience in Middle Age. By J. N. Morris and J. A. Heady.

Health Problems in the Manufacture and Use of Plastics. By Dr. Kenwin Harris.

Age and Work. A Study of 489 Men in Heavy Industry. By I. M. Richardson.

Miscellanea :

Charles Turner Thackrah in the Agitation for Factory Reform. By George Rosen.

A Mobile Consulting Room. By G. O. Hughes.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the abstracting journal* Abstracts of World Medicine, *published by the British Medical Association. The abstracts are divided into the following sections: toxicology; industrial physiology; industrial lung disease; industrial skin diseases; accidents and orthopaedic surgery; industrial ophthalmology; environment; general. Not all sections will necessarily be represented in any one issue)*

INDUSTRIAL TOXICOLOGY

Phosphorus Trichloride Poisoning in Industry. SASSI, C. (1952). *Med. d. Lavoro*, **43**, 298.

From the Industrial Clinic, University of Milan, 20 cases of phosphorus trichloride poisoning (one of them complicated by exposure to chlorine) occurring at a plant manufacturing this substance are reported; 3 of the cases are described in detail, and brief summaries are given of the other 17. There were no fatalities. No cases have previously been described in man, but references are given to experimental work on animals which established minimum toxic and lethal concentrations. Investigation showed that phosphorus trichloride was present in the atmosphere of the workroom in concentrations of 10 to 20 mg. per cubic metre under normal conditions and 80 to 150 mg. per cubic metre at times when the faults developed in the plant. In acute poisoning by relatively high concentrations the onset of symptoms was delayed for 2 to 6 hours; the main symptoms were acute irritation of the eyes and throat, photophobia, tightness of the chest, dry cough, dyspnoea, and generalized signs of bronchitis, with expiratory spasm developing later. Continued exposure to low concentrations produced symptoms after 1 to 8 weeks, mainly naso-pharyngeal irritation and cough, effort and nocturnal dyspnoea, and signs of bronchitis with expiratory spasm; after 1 to 2 years emphysema became marked. In both acute and chronic cases there were slight fever, moderate neutrophil leucocytosis, and some increase of bronchial shadows in the chest radiograph. Those who have experienced symptoms, whether acute or chronic, appear to be sensitive to further exposure, symptoms developing after 5 to 10 days of re-exposure.

The toxic action of phosphorus trichloride appears to be due to its decomposition into phosphoric and hydrochloric acids in contact with the skin and mucous membranes; the chemical reaction absorbs water from the tissues and produces intense heat, and it may be that the dehydration and production of heat are partly responsible for the symptoms. Treatment was largely symptomatic, with the addition of inhalations of alkaline and penicillin aerosols. Prevention could be secured only by the construction of a new plant with efficient exhaust ventilation; meanwhile reliance was placed on initial and period medical examinations, and the provision of respirators and protective clothing.

L. G. Norman.

Correlation of Blood Carbon Monoxide Level with Symptoms. ROBERTS, W. C. (1952). *Industr. Med. & Surg.*, **21**, 323.

In an instructive report of 26 consecutive cases of carbon monoxide poisoning, with recovery in every one, tables are provided showing: (1) the frequency of each sign and symptom; (2) a graphic summary of the results of the exposure together with the CO concentration in the blood at a stated time after exposure to the gas; and (3) the relation of duration of oxygen administration required to the blood CO content (which ranged from 30 minutes at 25% saturation to 70 minutes at 70% saturation). Treatment was with 100% oxygen, given with an oro-nasal mask, carbon dioxide not being used at all. The blood was tested for CO by the pyrotannic acid method, the technique of which is described. The CO content ranged from 20% saturation (in the only symptomless case) to 70%. Only in the one case at this highest level was a cherry-red colour of the face noticeable, mixed with cyanosis; this patient was in deep coma and during recovery he became disorientated, with hallucinations, delusions, and violent movements which were controlled only by heavy sedation; after 19 hours he had almost recovered. One man suffered respiratory paralysis without loss of consciousness. There was no close correlation of physical signs and symptoms with the blood CO level, other factors such as fatigue or debility intervening. In no case in which the level was below 50% saturation, however, was there either collapse or respiratory paralysis, nor was there unconsciousness when the level was below 60%. It is noted that with frequent small exposures a considerable degree of acclimatization may develop.

Appropriate precautions to be taken in factories producing carbon monoxide are: individual instruction of men exposed to risk both as to the danger and in the methods of resuscitation; provision of adequate oxygen inhalation equipment; insistence that every person about to enter a manhole or confined space must first test the air by a colorimetric method; provision of an alarm set to ring at a CO concentration of 400 p.p.m.; and the addition of ethyl mercaptan to the gas to provide a warning odour.

M. A. Dobbin Crawford.

INDUSTRIAL LUNG DISEASES

The Mobility of Pneumoconiotic Deposits. GROSS, P. and BROWN, J. H. U. (1952). *Amer. J. clin. Path.*, **22**, 821.

At the Mellon Institute and St. Joseph's Hospital, Pittsburgh, Pennsylvania, the authors have investigated the mobility of dust deposits in the lungs of animals and man. Antimony trioxide, iron oxide, and carbon dusts were administered to rats by inhalation and intratracheal injection. In the lungs of animals which died of incidental pneumonia the dust deposits were fragmented and "granular" and there were extracellular particles scattered throughout the alveolar exudate, whereas in the lungs of animals without pneumonia the dust was seen to be intracellular and in well-defined interstitial deposits

The human material was obtained from 83 consecutive routine necropsies. [It was therefore not from cases of pneumoconiosis in the ordinary sense of the word, though apparently all the subjects were town dwellers in an industrial area.] There were significant anthracotic dust deposits in the lungs in 78% of cases. In 20% the pigment deposits were sharp and smooth in outline, whereas in 58% they were ragged and granular. In the latter case extracellular particles were found in the surrounding alveoli and especially in sub-pleural deposits, and were also found invading the walls of blood vessels. Alveolar oedema was found in 80% of the cases with granular disintegration of the pigment deposits and in only 40% of the remainder.

The authors consider these appearances to indicate that mobilization of dust deposits occurs, and is due chiefly to the presence of oedema fluid. They claim that their observations show that dust particles can move through the lung tissue without being carried in macrophages, and argue that, if this is so, inhaled dust particles may enter the lung parenchyma without requiring transport by phagocytic cells. They also suggest that this further distribution of dust from the original foci of deposition in the course of pulmonary inflammation may account for the reputed severity of pneumonia in cases of pneumoconiosis, the dispersed dust particles being supposedly capable of producing inflammation in the new sites to which they are transported.

C. M. Fletcher.

Some Colloidal Properties of Inert Dusts. HOUNAM, R. F. (1952). *Arch. industr. Hyg. occup. Med.*, **5**, 375.

The author puts forward a theory (which he admits has been suggested before) that the apparent solubility of silica and other dusts is due to the presence of finely divided material and is therefore related to the dispersibility of the dust. The dispersibility can be measured directly by preparing suspensions of the dusts and studying their rate of clearing. Alternatively, it may be measured in terms of the "methylene-blue figure," that is, the amount of methylene blue needed to produce precipitation of a stable suspension of the dust by neutralization of the charges carried by its particles.

Experiments are described in which various dusts and mixtures of dusts were tested in this way, mineral dusts such as silica, alumina, and slate being suspended in water and the carbonaceous dusts such as carbon black, anthracite, and bituminous coal in 50% alcohol, since they are not wetted by pure water. [No details are given of the particle size distributions of the dusts tested, which do not appear to have been determined.]

In a further discussion of the theory that the solubility of dusts is really a measure of the amount of fine material in suspension, the author recognizes the difficulty of reconciling it with the evidence of King (*Biochem. J.*,1939, **33**, 944) that the molybdate method of measuring silica solubility is insensitive to particulate silica; nevertheless he claims that "the results of certain experiments are more satisfactorily accounted for by assuming that the very fine silica particles do give a colour reaction with ammonium molybdate". He then goes on to attempt to correlate his findings with the toxicity of the dusts and suggests that the greater the negative charge carried by the particles, the more toxic the dust, the particles of those dusts which are generally considered harmless being uncharged or carrying a positive charge. In support of this theory he gives methylene-blue figures for silica, anthracite, steam-coal, and bituminous-coal dusts, the last three coming from collieries "where the incidence of pneumoconiosis may be described as high, medium, and low respectively".

The figures given, interpreted according to the author's theories, suggest that silica and anthracite are of almost equal toxicity, while steam coal is much less toxic and bituminous less still, whereas on the basis of dispersibility, steam-coal dust should be much less toxic than the others.

[The author, in common with many others, neglects the possibility that the differences in incidence may have been due to differences in the concentration rather than the composition of the dusts in the collieries. The assimilation of the toxicity of silica and anthracite is contrary to all pathological evidence, and the differentiation of anthracite, steam, and bituminous coals is contrary to the finding by Heppleston (*Arch. industr. Hyg. occup. Med.*, 1951, **4**, 270) that the tissue reactions to these three dusts in the lungs of coal-miners are indistinguishable. It is difficult, however, to take this paper seriously, since the experimental results are presented in such a way that it is impossible to judge of their validity, and in any case frequently appear to contradict the author's own thesis, which is itself so vaguely expressed as to be almost meaningless.] *B. M. Wright.*

The Toxicity of Inhaled Aluminium Hydrate and its Action on the Pulmonary Tissues. JULLIEN, G., VALLECALLE, E., and LEANDRI, M. (1952). *Arch. Mal. prof.*, **13**, 31.

The authors review previous work on the effect of aluminium on the solubility of silica and on experimental silicosis. They consider also the various attempts to apply these findings in the field, the criticisms of them which have been made, and especially the claims of some German workers that aluminium is itself capable of

producing pulmonary disease. They then report the results of an experimental study of the effect of inhalation of aluminium hydroxide powder on the lungs of guinea-pigs. The animals were "exposed to inhalations of aluminium hydroxide ranging from 5 to 90 hours for a week to 7 months" [the meaning of this statement is obscure in the original; no details of the method of exposure are given]. The animals' lungs showed the usual reaction to dust inhalation, namely, the presence of dust cells in the alveoli and the peribronchial and perivascular deposits. Various other reactions were observed of which the most important was a thickening and hyperplasia of the alveolar walls. The authors discuss their findings and conclude that although no fibrosis was produced, aluminium hydroxide is potentially toxic when inhaled. *B. M. Wright.*

Does Silicosis Protect against Carcinoma of the Lung? SPÖRLEIN, S. (1952). *Zbl. allg. Path. path. Anat.*, **89**, 197.

Silicosis was found in 383 cases out of 24,571 necropsies performed at Wurzburg University between 1930 and 1947. In only 7 (1·8%) of these 383 cases was there evidence of bronchial carcinoma. On the basis of previous statistics it is calculated that five to six times as many might have been expected if the presence of silicosis were without effect on the occurrence of carcinoma of the lung.

Further evidence of such an effect is supplied by the relationship between the incidence of bronchial carcinoma and the severity of the silicosis. There were 5 cases of bronchial carcinoma among 91 subjects with slight silicosis, 2 among 105 with moderate silicosis, and none among 187 with severe silicosis. It is concluded, therefore, that contrary to the findings of Klotz, but in agreement with those of Meiklejohn, of Leicher, and of Ehrhardt, silicosis, and consequently silicic acid, far from predisposing to the development of bronchial carcinoma, definitely protects against it. *J. R. Bignall.*

Deposition of Siliceous Dust in the Lungs of the Inhabitants of the Saharan Regions. POLICARD, A., and COLLET, A. (1952). *Arch. industr. Hyg.*, **5**, 527.

A short description is given of the pathological findings in the lungs of 4 men with a history of lifelong exposure to dust clouds in the Sahara desert. While most of the dust particles in these clouds are of large size, there is also a fine component with particles less than 3μ in size. Only this fine dust can penetrate to the alveoli and cause pathological changes. The particles contain quartz, as shown by *x*-ray diffraction. The larger particles (which are assumed to be of the same composition) contain 80 to 88% silica, 2·5 to 4·6% ferric oxide, and 7·4 to 9% calcium carbonate. Histological examination of the lungs showed no pulmonary reaction of the classical silicotic type associated with the dust deposits. The changes were similar to those seen in coal-miners' lungs, except that there was much less dust. [The amount of dust in the lungs was not measured.] An injection of fine particles from the desert sand into the peritoneum of (unspecified) animals caused only a reaction described as "inert". The authors conclude that although the dust is composed of free crystalline silica, it is harmless to the tissues, and they propose two possible explanations: (1) That the dust is not "freshly fractured" and has become inert through weathering. [The authors here make no reference to the article by Wright (*Nature, Lond.*, 1950, **166**, 538) in which this argument concerning the different effects of "old" and "new" quartz is effectively discredited.] (2) That toxicity of the free silica is reduced by the presence of iron. *C. M. Fletcher.*

Tomography in the Investigation of Pneumoconiosis. BELAYEW, D. (1952). *Arch. Mal. prof.*, **13**, 257.

Tomographs were taken in cases of coalminers' pneumoconiosis at various stages and examined at the Institute of Hygiene in Mines, Hasselt, Belgium. In the micronodular and nodular stages tomography had little to add to the plain radiograph. In cases with early coalescent shadows tomography usually showed more extensive areas of condensation than would be expected from the plain film. Occasionally an extensive shadow in the plain film was shown by tomograph to be due only to pleural thickening. Tomography may also reveal that the shadow is due to the reinfection of an old scar. [The author does not say on what basis this distinction is made.] In cases with massive shadows the chief interest is the demonstration of tuberculous complication. [Apparently the author considers cavitation to be evidence of tuberculous infection despite a negative sputum.] Tomography also enables the exact disposition of the massive shadows to be more clearly appreciated, and it delimits emphysematous bullae and reveals bronchial distortion. Focal emphysema as described by Gough has not yet been demonstrated by tomography.
C. M. Fletcher.

NEOPLASM

Cancer and Industrialization. KÖRBLER, J., and FRANK, P. (1952). *Z. Krebsforsch.*, **58**, 589.

In the period 1931–50 at the Radium Institute of Zagreb 8,721 patients (4,463 males and 4,258 females) received treatment, of whom 8,543 had cancer and 178 a precancerous condition (chronic mastitis and adenoma of the breast). In males the incidence of cancer was highest in the skin of the face (2,022 cases), followed by cancer of the lower lip (1,266), larynx (349), tongue (282), rectum (231), oesophagus (207), upper lip (95), and breast (11). In females the order was: cancer of the skin of the face (2,453), breast (971), rectum (207), lower lip (191), upper lip (123), chronic mastitis (97), adenoma of the breast (81), cancer of the tongue (67), oesophagus (50), and larynx (18). Thus cancer of the lower lip, tongue, oesophagus, and larynx occurred in a much greater number of males than females.

The average age of the patients for each of the cancer sites ranged between 60·0 years (cancer of the skin of the face) and 52·8 years (cancer of the breast) in males, and between 59·1 and 51·4 years (for the same sites) in

females. There was little difference in the average age between males and females for any cancer site, except cancer of the tongue (males 58·4 years, females 53·3). The average age for adenoma of the breast was 40·7 years, and for chronic mastitis 38·6 years. If these conditions are accepted as being precancerous, it seems that, on the average, chronic mastitis becomes adenomatous in 2 years and cancerous in 13 years. The maximum risk for any site of cancer in both sexes occurred in the age range of 50 to 60 years. The range for adenoma of the breast and chronic mastitis was 30 to 40 years.

The number of cases of cancer seen increased each year during the period of study. It was postulated that if this increase were related to the increase in industrialization which took place during this time, the average age of the patients should be lower at the end of the period than at the beginning. The data were therefore grouped into four 5-year periods and the average ages in the 1st and 4th periods were compared for each cancer site. In males with cancer of the breast, the numbers were too small for statistical analysis. For chronic mastitis and adenoma of the breast the third and fourth periods were compared. In none of the groups, except in that of neoplasm of the breast, was there any significant difference in the average age. For cancer of the breast in females and adenoma of the breast there was a significant increase in the average age, and for chronic mastitis there was a significant decrease. *M. Lubran.*

Occupational Skin Cancer in a Group of Tar Workers. FISHER, R. E. W. (1953). *Arch. industr. Hyg. occup. Med.*, **7**, 12.

The author reports the result of a survey made by him of 241 men employed in a tar distillery in south London. Distillation of the tar was by the carbonization of coal in horizontal retorts. The aim of the survey was to observe the relation if any, between the condition of the skin of each man and the occurrence of tar warts or epitheliomata, and in particular to determine whether proneness to these lesions could be determined before employment or early in the man's working life.

For the purpose of the inquiry, skin changes due to tar were classified as : (1) affections of the follicles ; (2) acute tar erythema ; (3) pigmentation and chronic erythema ; (4) chronic tar dermatosis ; and (5) tar warts and epitheliomata. Chronic tar dermatosis was further subdivided into : (*a*) alteration in skin texture (*b*) ; simple plane warts ; (*c*) rough hyperkeratoses ; (*d*) freckles ; and (*e*) capillary telangiectases. Rough hyperkeratoses, which show as hard, irregular-shaped, gray or black collections of keratinous material with the appearance of being laid on the skin, are fairly common in tar workers but, according to the author, they are not tar warts. Furthermore, he agrees with Bettley that it is not possible to differentiate clinically between a typical tar wart and an early squamous-called tar epithelioma. The carrying out of the survey and its value were greatly helped by the fact that records of tar warts in this group had been kept throughout the preceding 25 years.

Of the 241 men, 66 had one or more tar warts, the total number being 422 warts. In one case warts occurred after only 11 months' exposure, whereas in another case the first wart did not appear until after 41 years' exposure. A workman with 26 years' exposure had had 63 warts, while another during 50 years had had 54. Investigation of the site showed that 70% of the warts occurred on the head and neck, and 28% on the forearm and hand, with none on the palmar surface of the hand. In only 7 cases (1·7%) was the wart on the scrotum, a figure much lower than that given in other published series. Lastly the author found no evidence that fair-haired men are more prone to tar warts, as has been asserted, than are dark-haired men, nor does chronic " tar skin " in his experience, necessarily precede the development of warts. There was, however, significant evidence to show that susceptibility to acute tar erythema is related to susceptibility to tar warts.

[Readers may be interested to note that the causes of death, with special reference to cancer of the lung, among the pensioners of his company have been analysed by Doll (*Brit. J. Indust. Med.*, 1952, **9**, 180).] *A. Meiklejohn.*

Cancer of Skin and Occupational Trauma. DOWNING, J. G. (1952). *J. Amer. med. Ass.*, **148**, 245.

The author reviews the present position of the notification of industrial disease in the United States. [It is obvious from his remarks that this group of diseases is not so widely recognized there as in Great Britain, and as many of the facts he mentions are already well known in Europe it would not be profitable to discuss them.] The recorded cases of occupational skin cancer in the U.S.A. are extremely few : 71 cases due to tar and pitch, 62 to grease and oil, 45 to exposure to *x* rays, and 18 to arsenic. In the author's view the small number is because so few have been notified in the past. Several case histories of carcinoma of the skin due to tar, arsenic, and grease seen by him personally are given.

Physical trauma as a cause of skin cancer is much more difficult to assess, and the aetiology is not so well understood as in the previous group. The author records a number of cases ; in the majority of these the trauma was repetitive, or else the cancer arose at the site of a burn received many years before. These cases are particularly difficult to assess legally. Finally, the urgent need for abolishing risks from the use of known carcinogenic agents is emphasized. *E. C. B. Butler.*

Exfoliative Cytological Control in Occupational Cancer of the Bladder. CRABBE, J. G. S. (1952). *Brit. med. J.*, **2**, 1072.

The ease with which exfoliation into the urine of cells from bladder tumours occurs has been utilized for the early diagnosis of these tumours. The author has applied Papanicolaou's technique to the study of samples of urine from about 1,000 dyestuff workers ; the methods of preparing specimens by sedimentation and the fixation and staining of smears are described in detail. The criteria of malignancy proposed by Papanicolaou and his system of grading cell characters as an aid to diagnosis are reviewed.

Of the 1,000 samples of urine examined, 26 gave suspicious or positive results. These findings were confirmed in 19 cases, and 4 were found to be false on cystoscopy. At the time of the report one false negative result had been detected.

The value of the method is emphasized, since 6 cases of bladder tumour were diagnosed by the smear technique alone and confirmed by cystoscopy even in the absence of haematuria or other signs of bladder disease. The author states that long experience is required for correct diagnosis in these cases since tumour cells may be confused with atypical non-malignant cells arising from other causes. Yet it has been found possible to diagnose a bladder tumour by the presence in the smear of a number of single cells alone, unaccompanied by clusters of malignant cells or by small fragments of cancerous tissue. Intensive application of this technique is recommended to run parallel with the search for microscopic haematuria.

Six photomicrographs of stained smears are reproduced. *H. G. Crabtree.*

OCCUPATIONAL DEAFNESS

Deafness in Shipyard Workers. Critical Evaluation of Findings in Six Hundred Cases and Diagnosis of Occupational Deafness. GOLDNER, A. I. (1953). *Arch. Otolaryng. (Chicago)*, **57**, 287.

In this paper is described a study of 600 deafened shipyard workers at Flushing, New York. The author, after referring to work published on the effects of excessive noise in military personnel, points out that the " acoustic hazard " of a pneumatic tool on metal is much the same as the chatter of a machine-gun or an automatic rifle. Hazard is increased when work is done inside a metallic chamber, and the smaller the chamber the greater the risk. Of the 600 patients, 403 had an occupational deafness with the typical audiometric curve ; in this group were included some who had a low-tone loss without any other cause than noise to explain it, and elderly men in whom the presence of presbyacusis was not clinically confirmed. In the remainder, except for a group of 35 " miscellaneous " cases, there was evidence that an occupational cause together with some other factor was responsible.

Patients with uncomplicated occupational deafness usually complained of deafness and tinnitus, though they seldom noticed the deafness until it was severe. Tinnitus was often more troublesome than deafness, but tended to be less noticeable after years of exposure. Occasionally vague otalgia was complained of. The audiometric curve was of the usual cochlear type, with a fall at first in the region of 2,000 cycles per second (c.p.s.), dropping further at 4,000 c.p.s. ; sometimes with a rise for higher tones and with progressive shortening of bone conduction. The greatest loss seems to occur in the first 5 years of employment ; after that, progress slows down until 20 years or more have elapsed, when normal age change must also be taken into account. The whisper is lost long before the conversational voice range is affected.

It is suggested that early " fatigue reaction " might be used as a screening method for eliminating workers who would be particularly sensitive to occupational noise. From the author's survey it seems that a pre-existing perforation of the membrane (it is noted that welders not uncommonly suffer from perforation by flying splinters) increases the hazard. On the other hand, patients with an established conduction deafness, such as that due to otosclerosis, are not usually so susceptible to loud noise. Nevertheless, such patients are not immune, and severe acoustic trauma may increase their deafness by adding a cochlear element. In some cases head injury, of which there were 27 cases, seems to have accelerated the progress of the deafness, or even to have started it ; it is pointed out that there need not be any fracture of the base of the skull in such cases. In one case there was evidence that a sudden " explosive-type " sound increased an already present occupational deafness ; in this instance the ear was pressed against a bulkhead when the full impact of a " chipping gun " struck the other side of the bulkhead.

Methods are suggested for diminishing the incidence of this trouble, among them pre-employment examination, elimination of " poor risks ", improved industrial design and sound-proofing, and the provision of efficient ear-protectors. *F. W. Watkyn-Thomas.*

Occupational Deafness among Textile Workers. MANCIOLI, G., and PESTALOZZA, G. (1953). *Med. d. Lavoro*, **44**, 134.

An investigation was carried out into the incidence of deafness among workers employed in the weaving sheds of 3 Milan textile factories and exposed to noise ranging between 96 and 102 db. in intensity. Of 96 workers examined, 77 had no signs of middle-ear deafness, but showed the well-known picture of occupational nerve deafness. In early cases a dip occurred in the audiogram at 4,096 c.p.s., and all audiograms showed a downward slope from 2,048 c.p.s. onwards. The element of fatigue was clearly shown in the difference between the acuity of hearing when the test was made before work started in the morning and that found in the same subject at the end of the day. This was very marked in recruits to the industry, in whom the audiogram returned almost to normal after 12 hours' rest. Workers who had been in the industry for many years showed a fatigue element as well as a permanent loss of hearing for high tones.

The noise in weaving sheds can be greatly reduced by improvements in design, but since these are unlikely to be widely introduced the authors recommend the individual protection of workers by means of a low-pass filter. For this purpose they have designed a soft rubber meatal insert with a mushroom-shaped plastic tube core. The use of this, they claim, would greatly reduce the damage to the cochlea. *S. A. Beards.*

Noise and Audiometric Histories Resulting from Cotton Textile Operations. COX, J. R., MANSUR, R. H., and WILLIAMS, C. R. (1953). *Arch. industr. Hyg.*, **8**, 36.

The effects on hearing of exposure to noise were studied in employees of a cotton textile mill in which,

since 1950, audiometric examinations have been made as a routine before engagement. A total of 54 subjects whose initial audiogram was normal were selected and retested 15 minutes and again 40 hours after ceasing work ; 18 of these worked in the weaving rooms, where the average background noise was 92 db., and 20 in the spinning rooms, where the average background noise was 85 db., the remaining 16 acting as a control group. The period of employment was in no case longer than 2 years.

No significant loss of hearing was found at frequencies below 4,000 c.p.s. among the weavers and spinners, but at that level weavers showed an average loss of 16 db. 15 minutes after ceasing work, and of 8 db. 40 hours after ceasing work. The spinners, exposed to less noise, showed an average loss of 7 db. 15 minutes after leaving work, with recovery almost to the control level after 40 hours respite from noise.

[The correction, derived from the audiograms of the control group and applied to those of the weavers and spinners, for differences in background noise during the three tests does not compensate for the very unfavourable conditions under which the tests were performed : moreover, the small size of the groups does not permit significant conclusions to be drawn from average findings. The paper therefore does not add very much to our knowledge of the subject.] *T. A. Clarke.*

Temporary Changes in Acuity of the Human Ear following Exposure to Intense Noise. GALLAGHER, J. B., and GOODWIN, J. E. (1952). *Arch. industr. Hyg. occup. Med.*, **6**, 332.

It is generally agreed that exposure of the human ear to intense noise for comparatively short periods will result in temporary diminution in hearing acuity. As a preliminary step in investigating this problem 47 subjects with normal binaural hearing acuity were exposed monaurally to wide-spectrum noise at approximately 115 db. above threshold for 10 minutes. The " normal " ear in subjects with slight unilateral high-tone hearing loss was similarly exposed. Auditory thresholds for 2,048, 4,096, and 8,192 c.p.s. were determined immediately before, and at varying intervals for about 20 to 30 minutes after, the exposure to noise.

After such exposure all ears tested showed temporary hearing loss for all three test tones : mean loss at 2,048 c.p.s. was 12·8 db., at 4,096 c.p.s. 24·9 db., and at 8,192 c.p.s. 25·5 db. All ears completely recovered normal acuity, usually within 30 minutes. Rates of recovery could in nearly all cases be correlated with severity of initial loss, but there were wide individual variations both in initial loss and in rate of recovery.

All 16 subjects with slight unilateral high-tone deafness and some of those with normal binaural hearing acuity had been previously exposed to high-level noise for various periods in industry or warfare. Although the previous exposures to noise were not subject to controlled observations, the findings in the present investigation are suggestive. While they do not prove, they do not refute the possibility that susceptibility to brief exposure to noise can be correlated with permanent hearing loss that may arise from noisy environments.

Norman W. MacKeith.

GENERAL

Visual and Orthopedic Defects in Civil Airmen. GILFORD, D. M., and STOVALL, W. R. (1951). *J. Aviat. Med.*, **22**, 442.

This paper is concerned with civil pilots who, despite some visual or orthopaedic handicap, have demonstrated their fitness to fly by undergoing flight tests under medical supervision ; 145 such pilots, the majority of whom had some defect of vision, were matched with a similar number of normal controls of about the same age and with approximately the same total flying experience. The incidence of accidents from all causes was then compared in the two groups.

The handicapped pilots suffered a total of 29 accidents affecting 27 pilots compared with 13 accidents affecting 11 pilots among the able-bodied group. When corrected for time of exposure these results showed that the defective pilots had an accident rate of 1·82 times that of the control group. Detailed analysis of the accidents, however, revealed that in very few cases did the physical defect bear any causal relationship to the accident.

P. Howard.

Pole Top and Other Manual Resuscitation Methods. A Comparison Study. GORDON, A. S., SADOVE, M. S., RAYMON, F., and IVY, A. C. (1952). *Industr. Med. & Surg.*, **21**, 147.

In an investigation carried out at the University of Illinois College of Medicine, Chicago, 5 normal, healthy, male volunteers were rendered totally apnoeic by the intravenous injection of thiopentone sodium and curare, and artificial respiration was applied manually by a number of methods to determine the efficacy of each. An endotracheal tube, secured by an inflatable cuff, was connected to a recording spirometer. The methods compared were those of Schafer and Howard, the Katsu, the pole-top technique of Oesterreich (for use in an emergency to resuscitate electrocuted linesmen), and various " push-pull " methods, namely, Silvester's method and the " arm-lift back-pressure " method.

The findings confirm those of previous experiments on living volunteers and on warm, non-rigid corpses, and indicate that push-pull methods give 2 to 3 times more ventilation than compression methods. For general use the authors recommend the arm-lift back-pressure technique as it is easy to teach and perform, is not unduly tiring, and is carried out with the patient in the prone position. The pole-top method, although a compression technique, gives reasonable pulmonary ventilation and is considered effective for its purpose. Silvester's method appears to come out of the comparison well, especially if practised with the victim's arms drawn right up above his head.

[The number of volunteers was small, and mean figures only are given for tidal-air estimations.] *J. N. Agate.*

Brit. J. industr. Med., 1954, **11**, 75.

TUMOURS OF THE URINARY BLADDER IN WORKMEN ENGAGED IN THE MANUFACTURE AND USE OF CERTAIN DYESTUFF INTERMEDIATES IN THE BRITISH CHEMICAL INDUSTRY

PART I. THE ROLE OF ANILINE, BENZIDINE, ALPHA-NAPHTHYLAMINE, AND BETA-NAPHTHYLAMINE

BY

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The Scope of the Report

The genesis, history, and achievements of the Association of British Chemical Manufacturers' research scheme for the investigation of tumour of the urinary bladder in a section of the chemical industry have recently been described in some detail by the Association (1953). The present paper is the result of a five-year field survey of the problem conducted in the factories of, and amongst the workpeople employed by, a group of interested member firms of the Association which had contributed towards the cost of the research. Part I has been written in two sections, the one, in narrative form, is the report proper and does not presuppose any detailed medical or statistical knowledge on the part of the reader ; the other is an appendix where some of the statistical manipulations to which the data have been subjected are set out in full. In Part II, which will be published in this journal shortly, the results relating to auramine or magenta reported herein will be considered in more detail. Both parts have been used as a basis for the recent legislation whereby tumour of the bladder occurring in certain occupations has been prescribed for benefit under the National Insurance (Industrial Injuries) Act (Statutory Instrument. No. 1740, 1953).

It was laid down in the terms of reference that the function of the field survey was to establish whether the manufacture or use of aniline, benzidine, α-naphthylamine or β-naphthylamine could be shown to produce tumours of the urinary bladder in men so engaged. Accordingly, the scope of this report has been limited to this topic, with but minor digressions to consider other possible causative substances. Furthermore, many medical aspects of the problem have been ignored or simplified. Both cancer of the bladder and papilloma of the bladder have been considered as an entity, after a purely statistical investigation to see that they could be so considered, and treatment has been ignored.

Historical

In 1895 the German surgeon Rehn reported what he considered to be an undue incidence of bladder tumours in a group of men employed in the manufacture of fuchsine (magenta), and he concluded that aniline was the most suspicious of the substances used in this process. From this supposition the term " aniline tumour of the bladder " stemmed, and has since become current in medical textbooks. Since this time there have been numerous reports from Great Britain, Germany, Japan, Switzerland, France, Italy, and America on this topic, and unanimity of opinion has been reached only about β-naphthylamine, which has been generally accepted as a cause of human bladder cancer. α-Naphthylamine has been suggested as a possible cause by some authorities, and strenuously denied this status by others. Those who believe that α-naphthylamine is dangerous seem to have tacitly accepted that the substance acts

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because it always contains a small proportion of β-naphthylamine. Benzidine has also been a subject of controversy, and, though American opinion on the whole seems to favour the theory that this substance is not a cause of bladder tumour, the opposite view seems to be held in Europe. There never appears to have been much evidence to implicate aniline as such, although the original observations on the manufacture of magenta were certainly valid.

Hueper, Wiley, and Wolfe (1938) conclusively showed that β-naphthylamine, in its commercially available form, caused bladder tumours in dogs, and Bonser (1943) confirmed these observations using a partially purified product. No convincing evidence of induction of bladder tumours by aniline, α-naphthylamine or benzidine in dogs or other animals has yet been produced although Baker (1950) claims bladder tumours in mice from 3 : 3′ dihydroxy 4 : 4′ diaminodiphenyl which he considered to be a metabolite of benzidine ; and Spitz, Maguigan, and Dobriner (1950) have induced tumours in other situations with benzidine itself. The evidence that pure β-naphthylamine or one of its metabolites are the only active carcinogens concerned in the production of tumours by this substance is not yet completely convincing, despite the work of Bonser, Clayson, and Jull (1951) who induced bladder tumours in mice by implanting paraffin wax pellets containing 2-amino-1-naphthol into the bladder, since Case and Pearson (1952) have demonstrated carcinogenic impurities in commercial β-naphthylamine and in what had previously been considered as " pure " β-naphthylamine. For the purposes of this report, therefore, the terms aniline, benzidine, and naphthylamine will mean these substances as encountered in industrial practice, and will not mean these substances as pure chemicals in the sense that an organic chemist might use such a term.

Goldblatt (1947) and Müller (1949) have reviewed the risk in industry at length, and Bonser (1947) has discussed the experimental aspects of the problem.

Sources of Information

The following sources of information have been available :—

Cases of Bladder Tumour in the Industry.—This is found in cases reported by firms ; cases found in hospital records and confirmed by firms ; cases found in hospital records and confirmed by the patient or near relative ; cases found from an examination of death certificates where the chemical industry was mentioned as the occupation of the deceased ; cases found from a cross-check between a nominal roll of persons known to be at risk and all the names collected by the means listed above ; cases found in coroners' records.

The Populations at Risk.—The firms participating in the scheme were asked to provide a nominal roll of all workers known to have had any contact with aniline, benzidine, α-naphthylamine or β-naphthylamine, stating the age of the worker and the dates between which he was exposed to these substances. Twenty-one firms complied with this request to the best of their ability, and a reasonably complete nominal roll from 1920 was compiled.

Natural History of the Incidence of the Disease in Males in General Population.—All death certificates mentioning bladder tumour for males dying in England and Wales between the years 1921 and 1949 were available. Many hospitals collaborated by allowing the use of their records for recent years.

Processes and Local Conditions.—All the participating firms cooperated by allowing complete facilities to inspect processes, and by collecting works-history data of cases known to have occurred in their factories.

Many other firms, members of the A.B.C.M. but not participating in the scheme, helped by giving information about ex-employees who developed bladder tumour.

The Nature of the Problem

Tumour of the urinary bladder occurs in both sexes in the general population. It is more frequent in males (about 2·5 males to 1 female) and is predominantly a disease appearing in the later years of life. Only 14% of all adult male deaths in England and Wales from the disease occur before the age of 55. Although the disease may be divided roughly into papilloma and cancer of the bladder, death certificates show that at death 88% of the deaths from bladder tumour are attributed to cancer and 12% to papilloma or benign tumour. This figure applies to all male deaths in England and Wales. In the cases found in the chemical industry this proportion is 94% cancer and 6% papilloma. This difference is of no statistical significance ; in other words, there is no special tendency for industrial tumours to be either more or less predominantly papilloma than non-industrial ones, as judged from death certificate data. The disorder, tumour of the bladder, must be regarded as a killing disease ; only 20% of all cases found by this survey in the dyestuffs industry survived more than 10 years from the first recognition of the disease. Since, as will be shown

later, the age of onset of the industrial form of the disease depends almost entirely on the age of entry into the relevant occupations, this high case mortality is serious. All patients who develop bladder tumour are not, of course, eventually certified as having a bladder tumour at death. Out of 819 cases notified by hospitals and known to be dead, 666 (81·3%) had a mention of bladder tumour on the death certificate.

Limitations of the Statistical Analysis

The accuracy of any statistical analysis is limited by the accuracy of the information upon which it is based. In the present study it often happened that the only data now in existence are those provided by the participating firms, and such data were not recorded for this purpose. Although such information has been examined most carefully as to its validity before incorporating it in this report, and where corroborative evidence, such as coroners' and factory inspectors' reports, was available, such additional information was always sought, the underlying possibility of inaccuracy must be borne in mind in interpreting the results.

There will be a tendency for the information to become less reliable as the period for which it is collected becomes more remote, and, as with some other occupational hazards which also occur in the general population, some of the cases which should properly have been assigned to occupational causes will have escaped notice as such, especially in areas of the country where medical opinion has not been focused on the hazard.

In the statistical analysis, only cases appearing on the nominal roll are used, and care was taken to ensure that no cases were placed on the nominal roll solely because it was known that they had developed a tumour. Thus, although in more remote times the nominal roll itself is too small, the tendency will always be to underestimate the industrial hazard through failing to trace all cases.

Certain conclusions drawn have only a statistical significance, with which implication the word is used in this report, therefore extrapolation from these conclusions should only be made with caution. For example, it will be shown that there is a slightly increased tendency for men entering the hazardous occupation at a more advanced age to develop tumours than for men entering at an earlier age. This does not necessarily imply any biological difference in susceptibility since, for instance, it could be explained on the hypothesis that older entrants are given more responsible jobs which would necessarily involve more exposure to the dangerous material.

Another example of the limitation of the term " significant " occurs where the statistical analysis of the data shows that the induction time* is independent of the exposure time. This does not mean that such a conclusion would be reached by animal experiments, or even by a very detailed analysis of short exposure times, but that within the rather coarse groupings of exposure times and induction times used, the two times are independent. Therefore it is legitimate to use the observed shape of the distribution of induction times as a basis for analysing the expected rate of appearance of cases.

The scope of the analysis is limited severely by the small number of cases that can be expected to occur since 1945, a date when, in accordance with earlier appreciation of the risk, certain sweeping changes in plant design were introduced. It is quite impossible at this stage to predict what effects these changes may have, and it will be realized that the slight reduction of risk noted in the post-1930 period is a mean value, and does not necessarily take into account the progressive results of these changes, which will have to await the judgment of posterity. Another limitation is the lack of knowledge of the relative importance of the different routes by which the dangerous substances may enter the human body, and of precise data about the operative concentrations of the substances met with and the amounts absorbed and eliminated.

Results

In all, by February 1, 1952, 455 cases of bladder tumour had been found in the British chemical industry. Four hundred and forty-four of these cases were found in and after 1921, the first year in which death certificates were available for a systematic search. Table 1 shows the distribution of these cases within the industry. Of the 341 cases occurring in employees of the member firms participating in the scheme, 298 (87·4%) had had contact with benzidine, β-naphthylamine, or α-naphthylamine, and only 32 (9·4%) were known not to have had such contact. It is necessary, as a starting point, to assess whether or not these 341 cases are more than could reasonably be expected by chance, on the assumption that the industry is exposed to only the same risk of developing bladder tumour as the general population. To do this it is necessary to form an estimate of the number of cases expected on this assumption, and this requires a knowledge of the population at risk. The nominal roll provides such knowledge in some detail, and of the 311 cases

* The length of time between first exposure to risk and the recognition of the tumour.

TABLE 1

THE DISTRIBUTION OF CASES OF BLADDER TUMOUR WITHIN THE CHEMICAL INDUSTRY

Date Group	Member Firms Investigated								All Others										Total All Groups	
	Contacts Include α-Naphthylamine, β-Naphthylamine, or Benzidine		Contacts Known not to Include α-Naphthylamine, β-Naphthylamine or Benzidine		Contacts not Known		Total		Employers not Known		Member Firms not participating in Scheme and not Investigated		Existing Firms not Members of A.B.C.M.		Firms no Longer Existing		Total			
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Before 1900	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1
1900–1904	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0	2	0	3	0	4
1905–1909	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	2
1910–1914	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1
1915–1919	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	2	0	3
†																				
1920–1924	0	3	0	0	0	1	0	4	0	8	1*	3	0	1	0	0	1*	12	1*	16
1925–1929	2	13	0	5	0	0	2	18	0	9	0	5	0	1	1*	3	1*	18	3*	36
1930–1934	3	18	2*	2	0	1	5*	21	0	11	0	6	0	0	0	1	0	18	5*	39
1935–1939	14	24	4	2	0	1	18	27	0	12	0	7	0	0	0	1	0	20	18	47
1940–1944	22	50	5	2	3	2	30	54	0	12	0	5	0	0	0	0	0	17	30	71
1945–1949	50	50	5	3	0	2	55	55	0	8	1	8	1	0	0	0	2	16	57	71
‡ 1950–	31	13	1	0	1	0	33	13	0	0	0	0	0	0	0	0	0	0	33	13
Total	122	176	17	15	4	7	143	198	0	65	2	34	1	2	1	9	4	110	147	308
Total	298		32		11		341		65		36		3		10		114		455	

Contacts include only α-naphthylamine of these three substances: 28

Contacts include only β-naphthylamine of these three substances: 59

Contacts include only benzidine of these three substances: 38

Contacts include two or more of these three substances: 173

Contacts include aniline (also auramine in two cases) but not magenta: 4

Contacts include magenta: 9

Contacts include auramine but not aniline: 4

Contacts include only substances not mentioned here: 15

Key: * Case where it is unknown if the patient has died.
† Death certificates not searched systematically until 1921.
‡ 1950 and subsequent death certificates not available at date of analysis.

which had had contact with aniline, benzidine, β-naphthylamine, or α-naphthylamine, 262 were persons whose names appeared on the nominal roll. This figure of 311 consists of 298 cases with contact with benzidine, α-naphthylamine, or β-naphthylamine, four with contact with aniline only, and nine with contact only with magenta.

A qualification for the nominal roll was that the persons must have been employed in the chemical industry for more than six months, though not necessarily in contact with the suspected substances. This limit was imposed because many firms did not provide records of men with shorter employment times, and, where such records were provided, a very large proportion of men worked for only a week or so. It was felt that these men would contain a high percentage of migrant types, whom it would not be possible to trace. The nominal roll used contains records of 4,622 men, who entered the industry at different times and at different ages.

Now it is not possible to estimate the number of cases of bladder tumour that would be expected from

the 4,622 men if no special risk were attached to their work, but it is possible to form a reasonable estimate of the number of death certificates mentioning tumour of the bladder which would be expected on this assumption (Case, 1953a, b). This expected number is between 3 and 5 for the 4,622 men, all due allowance being made for the age of the men and their date of entry into the work with the four substances mentioned ; and the number of death certificates mentioning tumour of the bladder found amongst the 262 cases whose names appear on the nominal roll was 127. There is therefore no doubt that a risk of dying of tumour of the bladder exists amongst that group of people who have had contact with aniline, benzidine, β-naphthylamine, or α-naphthylamine. In this group, that is those men who are known to have had contact with any of the four substances named and have been employed in the chemical industry for more than six months, even though their period of contact with any of the four substances was not necessarily six months, the data indicate that the overall risk of dying of bladder tumour is approximately 30 times that of the general population.

The Localization of the Risk within the Industry

It is now necessary to examine this group more carefully to see where the risk lies, and to see which of the specific substances mentioned can be implicated and which exonerated as causative agents. It seems very unlikely that the employees of the 21 participating firms could fairly be regarded as having equal chances of exposure to the suspected substances, but statistical analysis is hampered because no actual measure of exposure exists. It was therefore decided to consider the nominal roll in three sections, an arbitrary classification being made as follows :—

Group I.—The nominal roll of those firms which manufacture any one or more of the substances, aniline, benzidine, α-naphthylamine, β-naphthylamine ; it will of course consist of men exposed in both manufacture and use, since these firms also use these substances. This group consists of 3,198 men.

Group II.—The nominal roll of those firms which use but do not manufacture any of these substances, excluding those firms whose use is confined to the purification of the substances for sale as fine chemicals. This group consists of 1,275 men.

Group III.—The nominal roll of those firms which only purify any of these substances : this group consists of 149 men.

The distribution of the 311 cases of bladder tumour which had had contact with one or more of these four substances, with the number of death certificates mentioning tumour of the bladder expected and found, is shown for each group in Table 2 (Rank 9), and it is apparent that Groups I and II have an undoubted occupational risk of dying with bladder tumour. The one death in Group III is suspicious considering the low expectation of such an event.

It is convenient here to depart from a logical sequence of development, and to discuss an indication the justification for which will be dealt with more fully later. This is that the age of death was 51 in the one dead case in Group III, and that the age of onset was 29 in the other case. Both these ages are low compared with the most frequent age of death (65–70 years) or onset (60–70 years) found for bladder tumour in the general population and this fact lends weight to the suspicion that an occupational risk is operating.

Thus we may say that the occupational hazard at work is most intense in Group I, less so, but still definitely present in Group II, and probably still operating in Group III.

The Localization of the Risk to Particular Substances

It is now necessary to consider the evidence for the implication of each of these substances as a cause of bladder tumour, again using the death certificate criterion since this is the most precise measure available.

Aniline.—This is considered separately as a special case, since, as will be shown, the effect of the substance is different from that of the remaining three substances.

When the compilation of the nominal roll by member firms was first requested, the possible importance of magenta was not realized, but all manufacturers of magenta are automatically qualified for the nominal roll in virtue of the fact that they must handle aniline, and it is possible to divide the aniline nominal roll into two sections. (1) That derived from firms where it is known that magenta is not manufactured ; (2) that derived from firms where it is known that magenta is manufactured. Only a small proportion of the names on the second list will have been exposed to the manufacture of magenta. Ranks 1, 2, and 3 of Table 2 show the tumour cases and the expectation of death certificates from the aniline nominal roll divided in this way for the three groups of firms. It can be seen from these figures that there is not a sufficient excess of certificates found over certificates expected to

TABLE 2

THE NUMBER OF DEATH CERTIFICATES EXPECTED IF NO SPECIAL RISK WERE OPERATING AND THE NUMBER OF CASES AND DEATH CERTIFICATES FOUND FOR THE VARIOUS EXPOSURE CLASSES

Rank	Class	Group	Total No. of Cases Found	Cases on Nominal Roll			Cases on Nominal Roll where Death Certificate Mentions Bladder Tumour	Expected No. of Such Cases	% of Expected No. Derived from Incomplete Data	Significance of Difference	P
				Total	Alive	Dead					
1	Aniline without magenta contact	I	4	4**	2*	2*	1	0·30	35·8	None	>0·1
		II	0	0	0	0	0	0·23		None	>0·1
		III	0	0	0	0	0	0·01		None	>0·1
		All	4	4**	2*	2*	1	0·54		None	>0·1
2	Aniline with possible magenta contact	I	8	5	3	2	2	0·30	15·6	Suspicious	0·025
		II	1	1	0	1	1	0·05		None	>0·1
		III	0	0	0	0	0	0·00		None	>0·9
		All	9	6	3	3	3	0·35		Significant	<0·02
3	All aniline	I	12	9**	5*	4*	3	0·60	20·3	Suspicious	0·025
		II	1	1	0	1	1	0·28		None	<0·1
		III	0	0	0	0	0	0·01		None	<0·1
		All	13	10**	5*	5*	4	0·89		Suspicious	0·025
4	Benzidine	I	38	34	21	13	10	0·54	3·7	Very high	<0·001
		II	0	0	0	0	0	0·17		None	>0·1
		III	0	0	0	0	0	0·01		None	>0·1
		All	38	34	21	13	10	0·72		Very high	<0·001
5	α-Naphthylamine	I	28	19	13	6	6	0·66	3·2	High	0·005
		II	0	0	0	0	0	0·04		None	>0·1
		III	0	0	0	0	0	0·00		None	>0·9
		All	28	19	13	6	6	0·70		High	<0·005
6	β-Naphthylamine	I	59	55	28	27	26	0·30	4·1	Very high	<0·001
		II	0	0	0	0	0	0·00		None	>0·9
		III	0	0	0	0	0	0·00		None	>0·9
		All	59	55	28	27	26	0·30		Very high	<0·001
7	Mixed Exposures	I	162	135	50	85	75	1·15	13·5	Very high	<0·001
		II	9	7	0	7	5	0·32		High	<0·005
		III	2	2	1	1	1	0·006		Significant	0·005
		All	173	144	51	93	81	1·48		Very high	<0·001
8	All classes, excluding aniline	I	287	243	112	131	117	2·65	7·3	Very high	<0·001
		II	9	7	0	7	5	0·53		High	<0·005
		III	2	2	1	1	1	0·02		Suspicious	0·025
		All	298	252	113	139	123	3·20		Very high	<0·001
9	All classes	I	299	252	117	135	120	3·25	9·3	Very high	<0·001
		II	10	8	0	8	6	0·81		High	<0·005
		III	2	2	1	1	1	0·03		Suspicious	0·025
		All	311	262	118	144	127	4·09		Very high	<0·001

* also manufacturer of auramine.

warrant saying that aniline, as manufactured or used between 1915 and 1950, is a cause of bladder tumour.

Two other points require mention. (1) While, as the figures stand, there is only just enough excess of death certificates found over death certificates expected to be statistically significant in the magenta group, the whole picture is more strongly suggestive that magenta may be dangerous, since it is known that the nominal roll for the magenta group is much too large. (2) Two of the four cases occurring in the aniline group are also concerned with the manufacture of auramine, and there is some reason, as will be seen later, to suspect this substance.

Thus aniline, on present evidence, does not appear to be a cause of bladder tumour. If this conclusion is accepted for the purposes of this analysis, then men who have had contact with aniline and one other of the three substances benzidine, α-naphthyl-

amine, or β-naphthylamine, can now be allocated to contact with that other substance only.

α-Naphthylamine, β-Naphthylamine, and Benzidine.—The remainder of the 311 cases which had had contact with one of the four substances mentioned above can be subdivided into the following exposure classes :—(1) Those who have had contact with benzidine only of the three substances. (2) Those who have had contact with α-naphthylamine only of the three substances. (3) Those who have had contact with β-naphthylamine only of the three substances. (4) Those who have had a mixed contact with two or more of the three substances.

Ranks 4 to 8 of Table 2 show the tumour cases, the number with bladder tumour death certificates, and the number of death certificates expected if no special risk existed for these exposure classes and for the three groups of firms. These data show that benzidine, α-naphthylamine, and β-naphthylamine are associated with an increased death certification rate from tumour of the bladder. It will also be seen that only 2·6% of all the cases with bladder tumour death certificates would be expected to be of natural occurrence. If this ratio is even approximately valid for the remainder, it means that the whole group of cases can be considered as consisting of virtually only occupational tumours, and accordingly will be so considered.

It is necessary to examine the works history of the cases to see what types of job give rise to this risk. The nominal roll does not give full occupational details, so that differential rates cannot be obtained. The job-analysis of the 298 cases which had contact with one or more of the three substances under consideration is set out in Table 3 for each exposure class of substance and for each group of firms, and an inspection of Table 3 shows that the substances benzidine, α-naphthylamine, and β-naphthylamine can cause bladder tumour in workers engaged in

TABLE 3
JOB ANALYSIS

Job	Group	I					II	III	
	Manufacture (M) or Use (U)	Benzidine	α-Naphthylamine	β-Naphthylamine	Mixed	Total Group I	Total Group II	Total Group III	Total All Groups
Scientific staff	M	0	0	0	0	0 } 2	0	0	0 } 4
	U	0	0	0	2	2 }	0	2	4 }
Foremen	M	2	1	5	5	14 } 21	0	0	14 } 21
	U	0	1	1	6	7 }	0	0	7 }
Processmen, pressmen, filtermen, labourers	M	25	17	37	56	135 } 224	0	0	135 } 226
	U	8	5	9	67	89 }	2	0	91 }
Stillmen not included in above	M	1	2	0	1	4 } 4	0	0	4 } 6
	U	0	0	0	0	0 }	2	0	2 }
Weighmen	M	0	0	0	0	0 } 2	0	0	0 } 2
	U	0	0	0	2	2 }	0	0	2 }
Dryers and ovenmen	M	0	0	1	0	1 } 12	0	0	1 } 12
	U	2	2	2	5	11 }	0	0	11 }
Grinders	M	0	0	0	1	1 } 7	0	0	1 } 11
	U	0	0	0	6	6 }	4	0	10 }
Maintenance men, plumbers, and fitters	M	0	0	0	0	0 } 12	0	0	0 } 13
	U	0	0	4	8	12 }	1	0	13 }
Coopers and cask washers	M	0	0	0	0	0 } 3	0	0	0 } 3
	U	0	0	0	3	3 }	0	0	3 }
Total	M	28	20	42	63	153 } 287	0	0	15 } 298
	U	10	8	17	99	134 }	9	2	145 }
Total		38	28	59	162	287	9	2	298

either the manufacture or use of the material, and that the risk spreads through a wide variety of methods of coming into contact with the substances. A multiplicity of processes is covered by the jobs mentioned in the table, the extent of which is indicated by the following list.

Cases have been caused by the manufacture of both naphthylamines, their distillation, their flaking or stoving, their sulphonation, and the manufacture of sodium naphthionate ; the manufacture and use of the free bases, their hydrochlorides, and their sulphates.

The manufacture of benzidine and its isolation as the base ; the monohydrochloride, the dihydrochloride, and the sulphate, the use of benzidine and its salts.

The manufacture, drying, and grinding of finished colour prepared from the naphthylamines and benzidine, and the hand mixing of finished colour so produced.

The care and maintenance of plant for manufacturing the substances and for their sulphonation or conversion into finished colour.

The washing of casks contaminated with α-naphthylamine, β-naphthylamine, and benzidine, and the weighing out of these materials.

The purification of β-naphthylamine and benzidine, the total time involved being less than 100 working hours, has apparently caused one case, and longer exposure as a supervising chemist another case.

It is necessary to consider the characteristics of occupational tumours of the bladder in order that the course of events may be understood. The methods of determining the factors at work are technical, and the factors largely interdependent. It is therefore difficult to develop the argument in a strictly logical sequence ; some of the characteristics will be used before their meaning is discussed and, in general, the technical process of arriving at the characteristics will be dealt with in the statistical appendix. In these statistical procedures, unless otherwise stated, only the cases derived from Group I α- or β-naphthylamine, benzidine, or mixed contacts will be used. This is to avoid using a heterogeneous group, and to provide a standard measure of risk. The number of cases in the other two groups is too small to allow statistical conclusions to be drawn about the characteristics of induced tumours, but the cases can be used for comparison with Group I (see Table 9).

The first characteristics to be considered will be

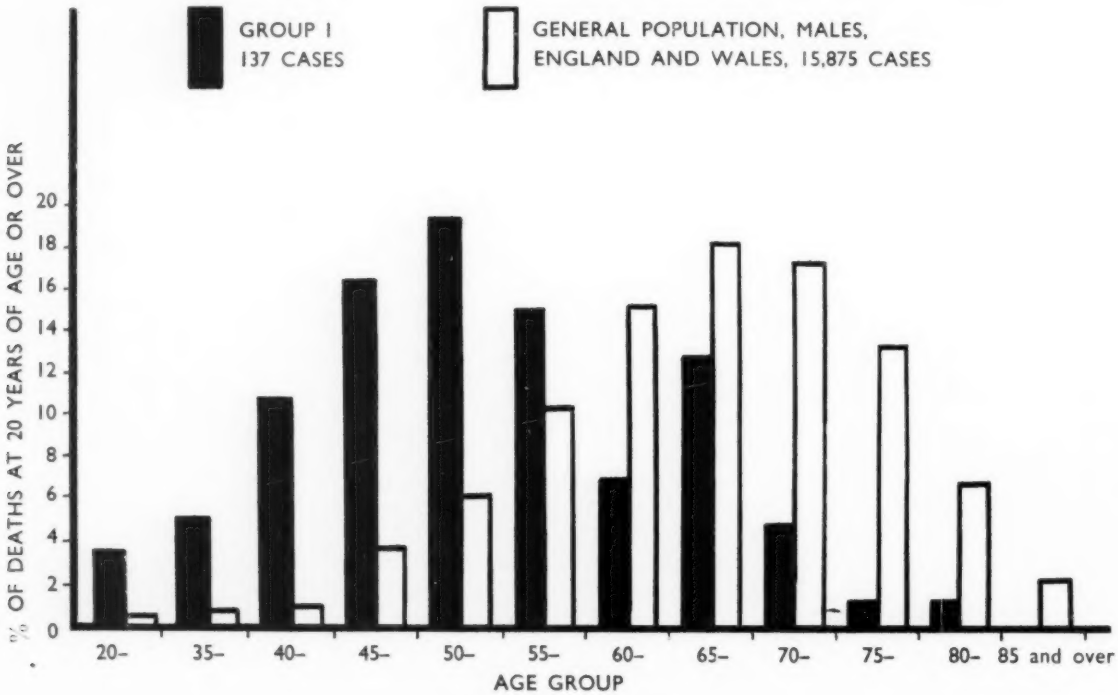

FIG. 1.—The age at death.

the age at which the tumours appear, and the length of time which elapses between the first exposure to risk and the recognition of the tumour. These will be termed the age of onset and the induction period respectively. The age at which naturally occurring tumours appear in the general population is required, but, since there is not enough information available to form a reliable estimate for the whole country, this cannot be determined at present, though such an estimate can be made for Birmingham and district (see Statistical Appendix). However, the age at death for all males in England and Wales whose death certificates mention bladder tumour can be determined for any year from 1921 to 1949, and therefore these figures are compared with the age at death of the 137 cases from Group I whose death certificates mention tumour of the bladder. (These cases are not all derived from the nominal roll.) Fig. 1 shows the percentage at each age group of the total number of deaths in each of these two groups for persons over 20 years of age.

It is shown that these 137 cases from firms in Group I died of bladder tumour at an earlier age than would be expected from the data relating to England and Wales, the most frequent age of death in the occupational group (50–55 years) being 15 years earlier than the most frequent age (65–70 years) in the general population. Thus the occupational hazard produces not only an increased number of deaths from bladder tumour, but also death from this complaint at an earlier age.

It now becomes pertinent to enquire whether this earlier age at death from bladder tumour is due first to a more limited survival time from the outset of the disorder ; secondly to a selectively greater susceptibility to the disorder in younger men ; and thirdly to a relationship between the age at exposure to risk and the age at onset, or whether some combination of these factors is at work. The first of these hypotheses cannot be tested directly by comparison with survival times since proper hospital records have not been available for a long enough period. An approximate answer can be given by comparing the age at onset of the group of chemical workers with the age at onset of a group of 750 male cases of bladder tumour reported from the Birmingham hospitals between 1936 and 1951. This comparison is given in Fig. 2, which shows clearly that the movement to lower age groups is still very marked, the most frequent age of onset of the chemical workers in firms in Group I (40–50 years) being 20 years earlier than the most frequent age of onset for Birmingham males (60–70 years). It is thus apparent that the earlier age at death is not due to a more limited survival time.

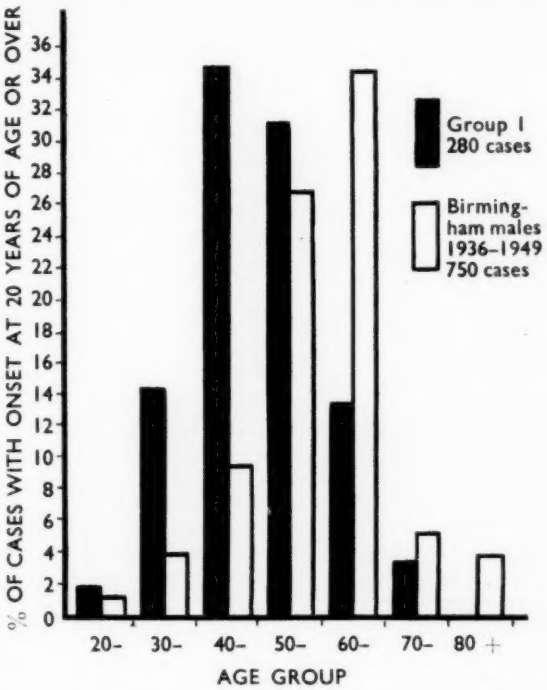

FIG. 2.—The age at onset. In a further seven cases, ages at onset were not known.

The second hypothesis was tested by calculating the number of cases that would be expected from persons entering any of the hazardous occupations (exposure to benzidine, α-naphthylamine, or β-naphthylamine) in the different age groups at the time of entry, on the assumption that this played no part in the production of tumours, and comparing the expected number with the number actually found, and these figures are shown in Table 4. It is shown that an older age of entry into risk increases somewhat the chance of developing a tumour, and therefore the earlier age of onset is not due to an increased susceptibility of younger persons.

The third hypothesis was tested by plotting the average age of onset against the age at entry in age groups. The result of this calculation is shown in Fig. 3. This shows that the age of onset is dependent almost entirely upon the age of entry, the induction period being nearly constant. The lack of complete agreement shown can be accounted for by the increasing loss of men who might otherwise develop bladder tumours by death from other causes in the older age groups. For all practical purposes, the younger a man is when he enters risk, the younger will he be when he gets a tumour, and the most common time to develop a tumour will be between

TABLE 4

NO. OF EXPECTED CASES IF AGE AT ENTRY HAD NO EFFECT ON INCIDENCE AND NO. FOUND

Age at Entry	Expected No. of Cases Allowing for Death from All Causes at 1931 Rates	Tumours Found
Under 20	22	13
20–	109	90
30–	74	75
40–	29	52
50–	5	8
60 and over	0	0
TOTAL	239	238
Unknown	—	5
	Total	243

$\chi^2 = 27{\cdot}6$
$n = 4$
$P < {\cdot}001$

15 and 20 years after starting work in the dangerous environment.

The apparent constancy of the average time from first exposure to development of a tumour for each age group of entry into risk suggested that the induction time should be studied further. Accordingly, the induction times of all cases in each exposure class were examined, and the average time and the scatter around it determined. The values are benzidine exposures 16 (S.D. 5) years, α-naphthylamine exposures 22 (S.D. 6) years, β-naphthylamine exposures 16 (S.D. 6) years, mixed exposures 18 (S.D. 7) years, and the mean for the combined series 18 (S.D. 7) years. The mean induction time for benzidine and β-naphthylamine is the same, but there is a real difference between this time and that for α-naphthylamine, where the mean time is six years (37·5%) longer. The spread of the induction times for all the cases pooled together is shown in Fig. 4. (The superimposed normal curve is discussed in the appendix.) This shows that while the most frequent induction time is between 15 and 20 years from exposure, tumours can develop within five years or after 45 years from the first entry into risk. This is of practical importance because it means that it is possible for a case of bladder tumour to be of occupational origin even if the induction time is very short or very long.

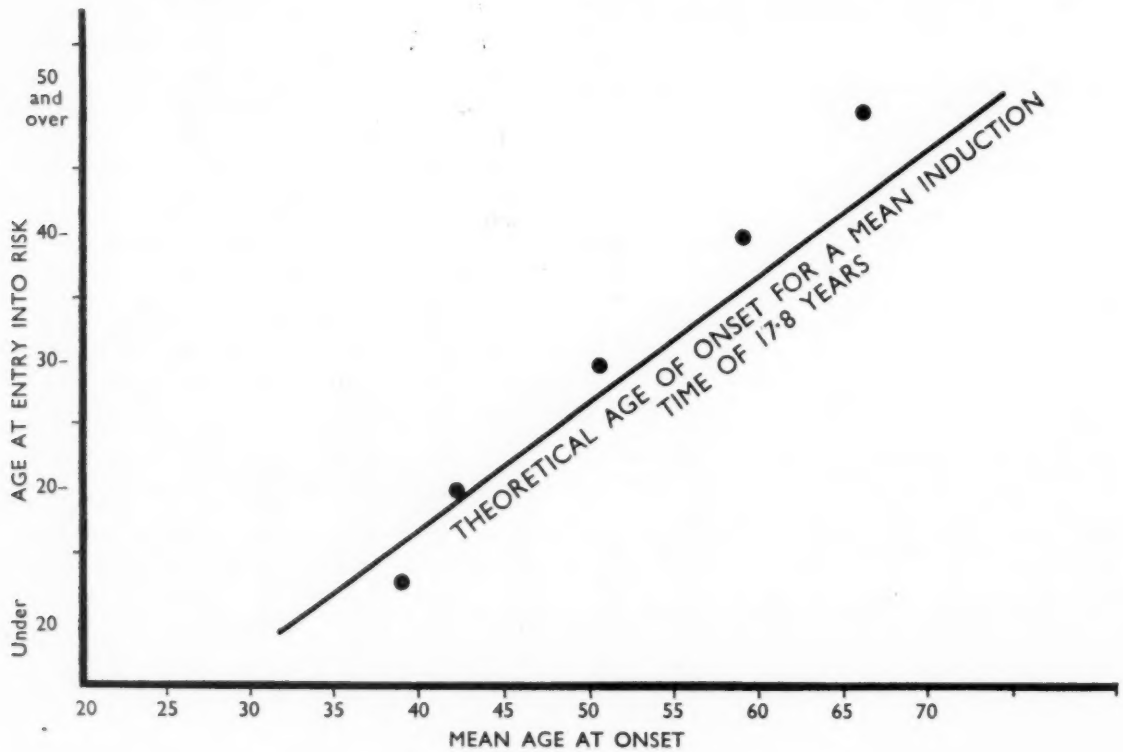

FIG. 3.—Age at entry and age at onset.

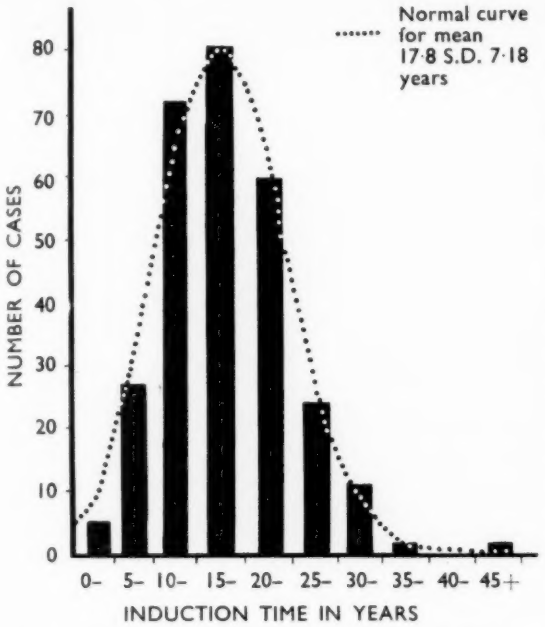

FIG. 4.—The distribution of induction times in Group I (281 cases). In a further six cases induction times were not known.

It is necessary to see whether the variation in induction time is an expression of the dose of the noxious material encountered. If it is such an expression, then men receiving a smaller dose should tend to get tumours after a longer interval, and men receiving a larger dose after a shorter interval. No direct measure of the dosage received is available but it is reasonable to suppose that the length of exposure will be some sort of indication of the amount of the substance encountered. However, there will obviously be a number of patients who have worked in the hazardous environment until the onset of the disorder, and here of course the length of exposure and the induction time will be identical. There will also be a number of men where the induction time exceeds the exposure time. In all, there are 281 cases in Group I where both the exposure and induction times are known. These 281 cases are shown in Table 5, subdivided into groups according to the length of the two times. The number of cases in each group that would be expected if the exposure time did not affect the induction time has been calculated and is also shown. The method of calculation is discussed in the appendix. There is no trend to suggest that there is an association between short exposure times and long induction times, or vice versa, and the deviations from the expectation are no more than could be reasonably attributed to chance variations of sampling.

Another more approximate measure of the severity of exposure might be the supposition that manufacturers of a substance will be more heavily exposed than users. If this is so and if the severity of exposure did affect the induction time, then the manufacturers should show a preponderance of shorter induction times and a shorter mean induction time. Table 6 shows the number of cases in each group of induction times that would be expected in users if severity of exposure had no effect, and if there were equal numbers of users and manufacturers, and also the number actually found. The observed differences are no greater than could easily occur by chance. The mean induction time of the manufacturing group (17·7 years) does not differ from that of the using group (18·3 years) by more than might occur by chance. Thus it may be concluded that the severity of exposure, as judged by these methods, has no effect on the induction time of the disorder. The mean induction time in Groups II and III combined, where, as will be shown later, the risk is much smaller, does not differ materially from these figures. It would therefore appear that this mean induction time is characteristic of the particular substance concerned, and not dependent on the severity of the exposure. The fact that, within the terms chosen for the analysis, these factors are independent makes it possible to use the observed distribution of the induction times as a basis for calculating the expected appearance of tumours, and the underlying principle of the subsequent analysis rests upon this independence.

Another implication of the independence is that the difference of the mean induction times for α-naphthylamine and β-naphthylamine suggests that the β-naphthylamine content of the α-isomer may not be the sole active agent, unless α-naphthylamine exerts a delaying action on the rate of development of β-naphthylamine tumours.

Severity of the Incidence in Population at Risk at Different Times

It is necessary to consider how the incidence in the population at risk varies at different times, and what factors influence this variation. Accordingly the nominal roll for Group I was divided into groups who started work in the hazardous occupations in the years 1910–1919, 1920–1924, 1925–1929, and so on in five-year groups to 1945–1949. Each group was further subdivided into the length of time which the man remained in the occupation. This subdivision was carried out for each class of benzidine

TABLE 5

NO. OF CASES FOUND AND EXPECTED IN EACH EXPOSURE TIME GROUP IF LENGTH OF EXPOSURE DOES NOT INFLUENCE INDUCTION TIME: GROUP I

Exposure Time in Years		Induction Time in Years							Total	χ^2
		0–	1–	5–	10–	15–	20–	30 and over		
0–	Found	0	1	0	2	1	3	0	7	$\chi^2 = 0{\cdot}30$ $n = 1$ $P = {\cdot}75$
	Expected	0·0	0·1	0·8	1·9	2·0	1·9	0·3	7·0	
1–	Found		4	10	9	12	19	0	50	$\chi^2 = 6{\cdot}36$ $n = 3$ $P = {\cdot}075$
	Expected		3·0	5·4	13·7	14·5	14·4	2·0	50·0	
5–	Found			17	20	12	9	0	41	$\chi^2 = 6{\cdot}66$ $n = 2$ $P = {\cdot}04$
	Expected			16·2	12·7	13·3	13·2	1·9	41·1	
10–	Found				41	8	7	1	16	$\chi^2 = 0{\cdot}00$ $n = 1$ $P = {\cdot}99$
	Expected				41·6	7·5	7·4	1·1	16·0	
15–	Found					47	11	2	13	$\chi^2 = {\cdot}007$ $n = 1$ $P = {\cdot}96$
	Expected					43·7	11·4	1·6	13·0	
20–30	Found						33	12	127	$\chi^2 = 5{\cdot}54$ $n = 4$ $P = {\cdot}25$
	Expected						43·2	6·2	127·1	
Total	Found	0	5	27	72	80	82	15	281	$\chi^2 = 2{\cdot}99$ $n = 4$ $P = {\cdot}6$
	Expected	0·0	3·1	22·4	69·9	81·0	91·5	13·1	281·0	

Total
$\chi^2 = 18{\cdot}87$ $n = 12$ $P = {\cdot}1$

The dotted lines indicate groups combined in carrying out χ^2 test which is discussed in the statistical appendix.

TABLE 6

THE EFFECT OF MANUFACTURING OR USE ON THE INDUCTION TIME

Induction Time (years)	Under 5	5–	10–	15–	20–	Over 30	Mean and S.D.
Cases found in the manufacturing group	2	18	38	47	35	9	18·18 ± 8·5
Cases in user group calculated for a group of equal size	3	14	35	43	43	11	17·63 ± 7·3
Difference of Distribution $\chi^2 = 4{\cdot}09$ $n = 4$ $P = {\cdot}4$	The dotted line indicates groups combined together in carrying out the χ^2 test.						Difference of means $\chi^2 = 0{\cdot}55$ $t = 0{\cdot}72$ $P = {\cdot}4$

exposure, α-naphthylamine exposure, β-naphthylamine exposure, and mixed exposure, and also for all these exposures pooled together. The cases derived from the nominal roll were arranged in similar subdivisions, so that the percentage incidence arising from each subdivision could be calculated. Fig. 5 shows the percentage of the population in each group according to the date of starting developing bladder tumour, irrespective of the date of tumour development, age at entry, or length of service. This figure is calculated from the pooled classes. (The superimposed cumulative normal curve is discussed in the appendix.) It is seen that as the date of starting gets earlier the percentage of the population affected gets larger, until a steady level of just under 20% of the original population being

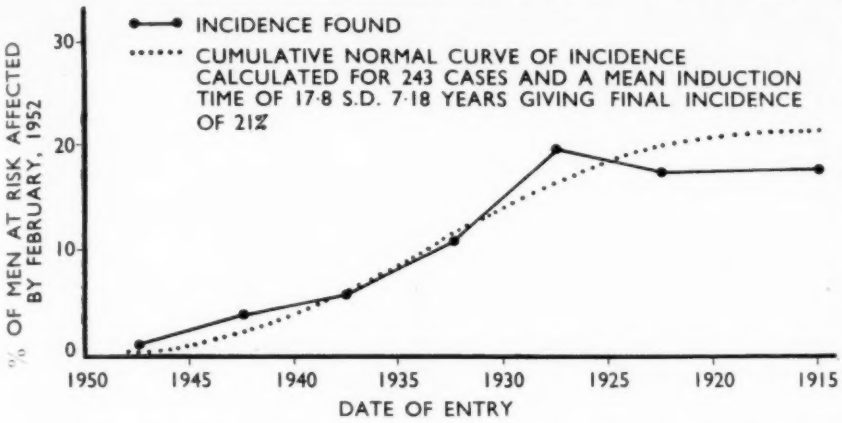

FIG. 5.—The crude incidence at different times. Pooled exposures in 243 cases of Group I.

affected is reached. It becomes necessary to find out which factors other than the induction times are responsible for the shape of this graph. It might be that in earlier times exposures were greater and protective methods less good ; it might be that men were exposed for longer periods in earlier years, or it might be that some combination of these factors is at work. It is also necessary to see whether each of the three substances produces a similar or dissimilar severity of incidence. Fig. 6 shows a graph for each of the four classes of exposure that were combined in Fig. 5. Although these graphs show obvious dissimilarity, a consideration of this must be postponed until the effect of the length of exposure has been evaluated.

There is already a suggestion that the severity of exposure affects the number of cases that will be found, since relatively fewer cases occurred amongst the employees of Group II and III firms. The length of exposure may, as said before, be regarded as some measure of the severity of exposure. The graphs already considered (Figs. 5 and 6) did not take any account of the length of exposure in each date group of entry into work. They may thus be regarded as being calculated from the mean effective exposure, which is defined as the length of time of exposure necessary for the particular class of exposure to produce the average risk for that class of exposure.

The number of cases of tumour occurring in each grouped length of exposure class, using the groupings shown, was found, and the figures expressed as a percentage of those expected if the length of exposure had no effect, i.e., the figure for the mean effective exposure is called 100%. The results of these calculations are shown for each class of exposure in Fig. 7. From this it can be seen that the length of exposure has in all classes a profound effect on the number of cases produced, and that the mean effective exposure is reached after a varying exposure time. It is also shown that the risk of developing a tumour increases to a maximum and then decreases for men who have been employed for a long time. This strongly suggests that for a given level of risk, where risk is the sum total of all factors causing bladder tumour, there are members of the population being considered who are susceptible to the disorder and members who are not. Altering the

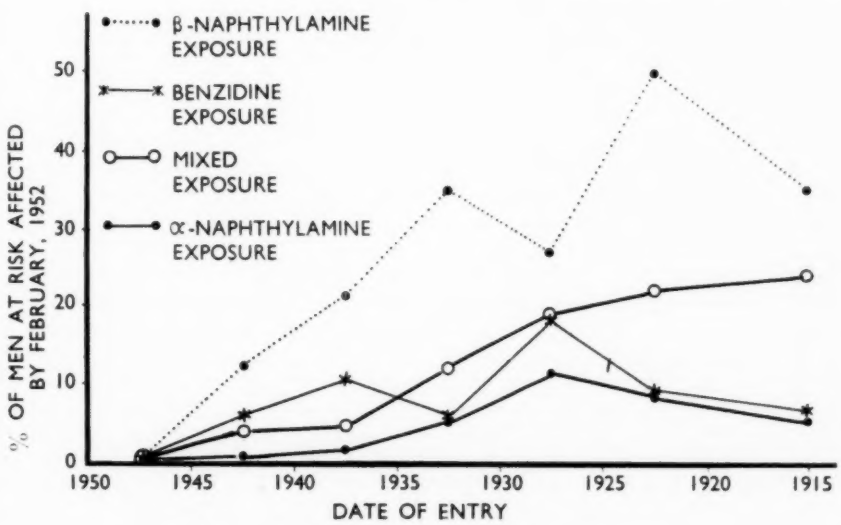

FIG. 6.—The crude incidence at different times by exposure class.

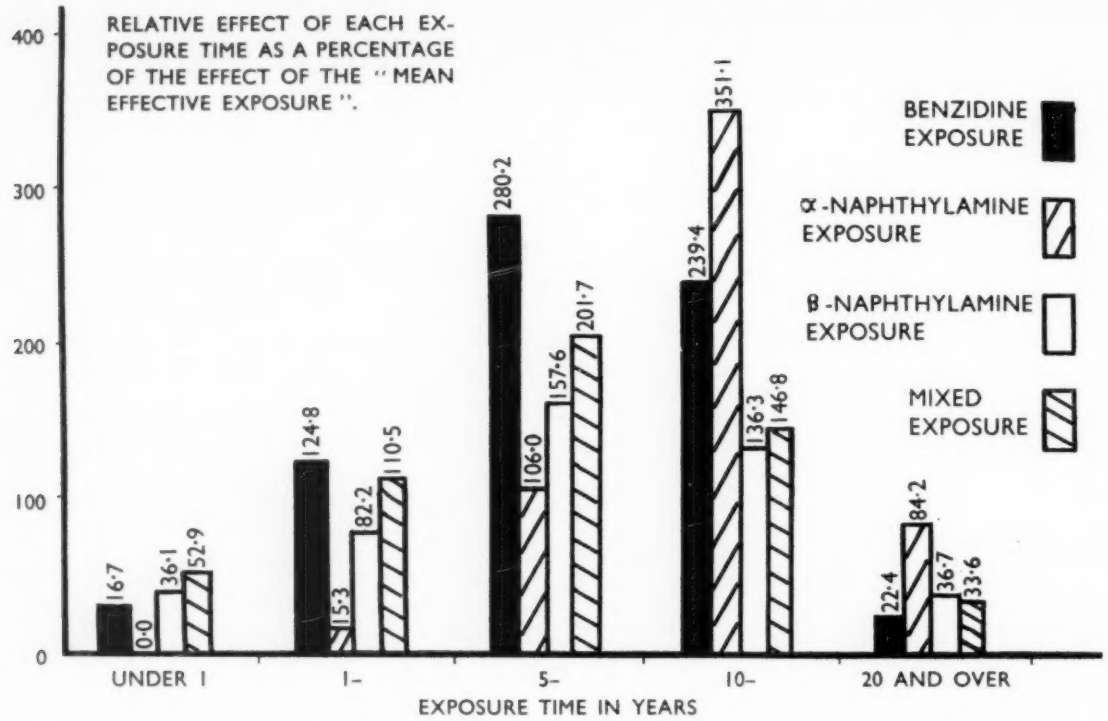

FIG. 7.—The effect of exposure time by exposure class.

level of risk will alter the relative proportions of these two groups, and it is probable that a high enough level would produce a 100% affected group and a low enough level an almost unaffected group. The fall in the severity of incidence after long exposure times means that most of the persons who will be affected have already contracted tumours, and so have been removed from the figures available for calculation. This apparent immunity is a statistical concept. It may be due to the fact that the population at risk consists of some who really have little or no contact with the substance concerned; that some of the men acquire a "know-how", either conscious or unconscious, that enables them to avoid risk; that inherently in themselves they possess a resistance; or that more than one of these factors is at work.

Whatever the actual explanation of the graph, from a practical aspect it means that exposures of less than one year to benzidine, β-naphthylamine, and mixed exposures have already produced sufficient effect to make it impracticable to attempt to obviate the risk solely by reducing the employment time. α-Naphthylamine appears to require a longer exposure for equivalent effect, but too much reliance should not be placed on the low incidence found at very short exposures, since the number of cases available for study is very small, and therefore the conclusions tend to be unreliable.

Applying this knowledge of the effect of the exposure time on the number of tumours produced, it becomes possible to represent graphically the tumour incidence that would occur at different times if all the exposures had been of the same length, namely of the mean effective exposure. In this way the number of tumours that would have occurred in the nominal roll for each class of substance had the men been exposed for the mean effective exposure to a standard substance that has a mean potency can be calculated, and is shown in Table 7. (A standard substance is defined as a hypothetical substance whose activity in the production of bladder tumours represents the average activity of the substances actually met with by the men at standard risk, and a mean potency as the average measure of the power of the standard substance, with exposure for the mean effective exposure time to produce tumours in a population at risk of known size observed from the date of entry into risk after 1910 until 1952.) A comparison of these numbers

TABLE 7
EFFECT OF THE EXPOSURE CLASS

Exposure Class	Benzidine	α-Naphthyl-amine	β-Naphthyl-amine	Mixed Exposures
No. of cases expected ..	47·0	46·9	25·5	124·0
No. of cases found ..	34	19	55	135
Relative potency	72%	41%	216%	109%
Ultimate relative potency	68%	58%	185%	127%

with the numbers actually found gives a measure of the relative potency of each individual compound expressed as a percentage of the mean potency; where the relative potency is defined as the average measure of the power, expressed as a percentage of the mean potency, of a specified class of exposure, with exposure for the mean effective exposure time for that class of exposure, to produce tumours in a population at risk of known size, observed from the date of entry into risk after 1910 until 1952.

Statistical tests show that this relationship between the substances held true generally over the period between 1915 and 1950. Thus it can be said that, under the exposure conditions obtaining in the Group I firms between these dates, β-naphthylamine has been the most potent cause of bladder tumour, followed by mixed exposures, then by benzidine, with α-naphthylamine the least potent of these substances. β-Naphthylamine has been about five times as potent as α-naphthylamine, and three times as potent as benzidine.

However, the differing mean induction times for the different substances suggest that this may underestimate the relative potency of the substances with the longer induction times. Therefore a measure, called the "ultimate relative potency", has been calculated and is necessary to express what these relationships would be when all the expected cases at the mean risk have developed, on the assumption that men die of all causes at 1931 rates. This measure is defined as the measure of the power, expressed as a percentage of the ultimate mean potency, of a specified class of exposure, with exposure for the mean effective time for that class of exposure, to produce tumours of the bladder in a population at risk of known size observed until all have died, on the assumption that death from all causes acts at the 1931 rate for males in England and Wales. These ultimate relative potencies are also shown in Table 7. It can now be seen that the relative potencies of α-naphthylamine and mixed exposures have been underestimated and that of β-naphthylamine overestimated by the relative potency figures.

Effect of Changing Conditions and Altered Techniques on the Incidence at Different Times

The only factors so far investigated that affect the final incidence of tumours are the type of substance encountered and the length of exposure. Fig. 8 shows what the result would be if all the men had been exposed to each exposure class for the mean effective exposure time, and, by the use of the potency factors, if all the men were working at the mean potency. This removes chance influences due to the number of men working on a particular substance at a given time, and to different movements of labour that may take place at different times. The incidence in the population at risk entering the relevant occupations at different dates increases, slowly at first, then more sharply, and then again slowly, with the passage of time since starting work. The highest figure reached is about 24%, and a time will come when the final incidence is reached since deaths from all causes will leave no more men in the original population to be affected.

The data that have been collected about the induction times make it possible to calculate a

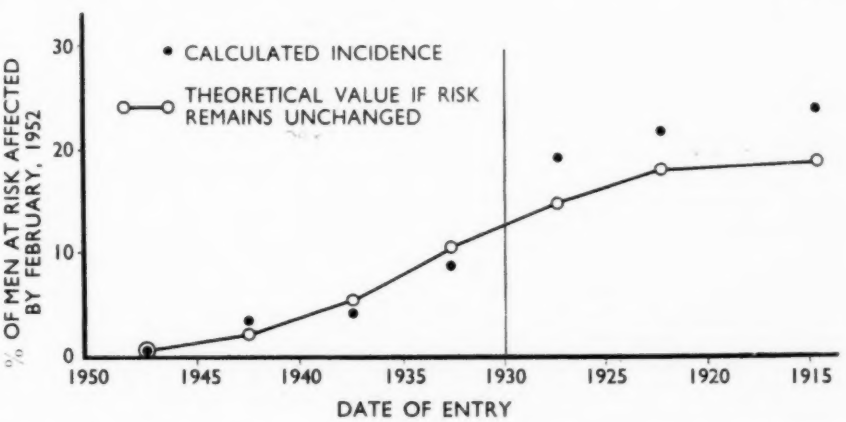

FIG. 8.—The incidence at different times calculated from the mean effective exposure time and the mean potency in 243 cases of Group I.

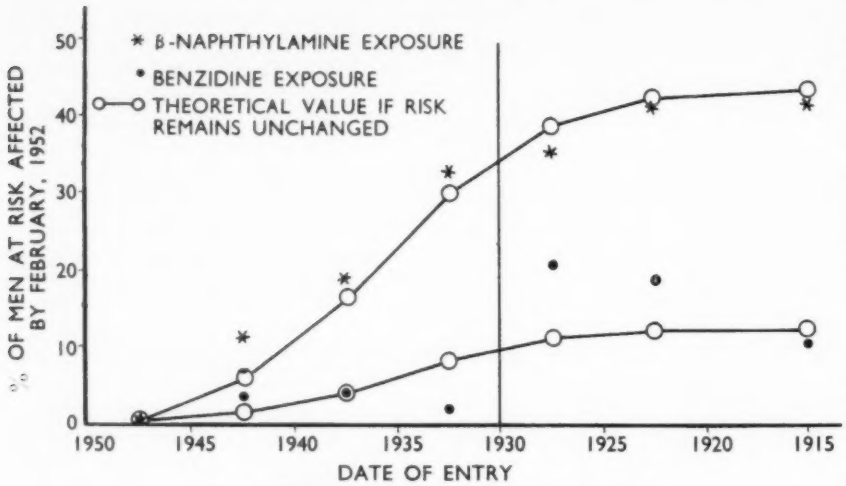

FIG. 9.—The incidence at different times by exposure class.

graph of the way in which the incidence figures would behave if it is assumed that the "danger-value" of exposure for a given time is constant between 1915 and 1950; in other words, that any alterations of plant and process have been without effect, and if it is further assumed that deaths from all causes affect the men at the rates found in the male population of England and Wales for 1931, this date being the nearest to the centre of the period being considered for which such information is available. Fig. 8 shows this curve as well as the values that were actually found.

Alterations of plant and technique which might be expected to have affected the risk were made first in about 1935, and developed progressively with additional impetus after 1945. Since it has already been shown that the full effect of exposure is not experienced until after an exposure time of more than five years, the men entering between 1930 and 1935 may be expected to benefit to some extent by any reduction of risk that has taken place between 1935 and 1940. If, therefore, this graph is considered as consisting of two groups of men, those entering before 1930 and those entering after 1930, it can be seen that the theoretical line underestimates the risk in the earlier period, and overestimates the risk in the later period. Statistical tests show that this difference of estimate is slightly more than could reasonably be expected to occur by chance. The analysis of the figures reveals that the mean post-1930 risk is about 66% of the mean pre-1930 risk, but it is safer to limit this conclusion more generally to stating that the risk is reduced just significantly. It is not possible yet to say that this improvement is progressive, since cases which may be expected to occur in men who entered after 1945 would be very few, and the results of improvements inaugurated then are not yet assessable.

How Individual Classes of Exposure Follow the Type of Theoretical Curve in Figs. 9 and 10

Figs. 9 and 10 show the theoretical expected incidence for the four exposure classes calculated on the assumptions that the risk remained constant throughout the whole period, and that the death rate from all causes was at the 1931 figure. The incidences actually found are also shown. An analysis of these curves shows that the mean post-1930 risks for benzidine and for mixed exposures are reduced by more than could be expected from chance sampling variations (to 39% and to 67% of the pre-1930 risk respectively) and also that the mean post-1930 risks for α-naphthylamine and β-naphthylamine have risen, being 118% of the

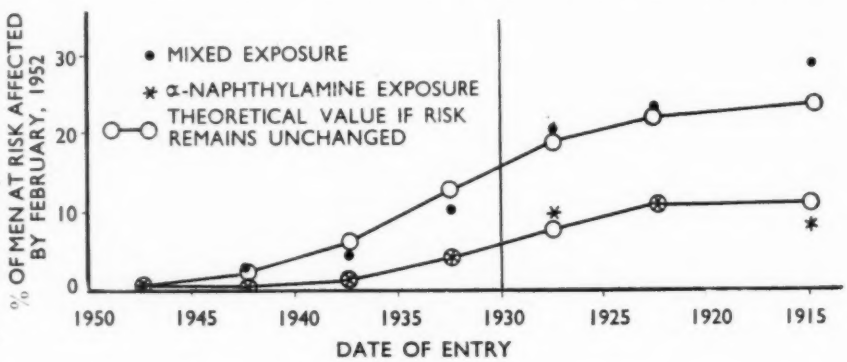

FIG. 10.—The incidence at different times by exposure class.

pre-1930 risk in each case, but this difference does not exceed what might be attributed to chance sampling variations. The slight total diminution of risk shown in Fig. 8 is derived from the benzidine and mixed exposures classes, though any quantitative estimate of the change should also be treated with reserve.

The theoretical graphs for the mean risk over the whole period conform reasonably closely to the curve that has been found for the exposure classes α-naphthylamine, β-naphthylamine, and (apart from the diminution of risk since 1930 already noted) mixed exposures. In the case of benzidine the scatter of the observed values around the theoretical graph will be seen to be greater. Detailed histories of changes in industrial technique are not available for all firms or for all of the exposure classes, but 68% of the benzidine cases are contributed by one firm, and were engaged in the manufacture of this substance. Scott (1952) has given a historical summary of the manufacture of benzidine by that concern. It is of interest to attempt to correlate this history with the graph of the tumour incidence for the exposure class benzidine, and this is done in Fig. 11. In drawing the comparison, the assumption has again been made that a change of process will affect men who entered in the five-year period before the change was made, but not men who entered more than five years previously. The figures given are the incidences found expressed as percentages of the incidences that would be expected if the risk had been constant throughout the period. The last three groups are combined because a comparison of cases with very low expectation figures is not precise, since the actual cases can only be whole numbers. There is a suggestion that the isolation of the base, as opposed to the conversion of the sulphate to the base, increases the risk. Such a deduction should be treated with reserve, since this type of analysis can be fallacious. There is not enough evidence to make any comment about the isolation of the hydrochloride.

HISTORY OF BENZIDINE MANUFACTURE (SCOTT, 1952)

BENZIDINE PROCESS : ZINC REDUCTION.
PRODUCT ISOLATED AS :—

1950	1945	SULPHATE	1940	1935	1930	1925	SULPHATE	1920	1915
HYDROCHLORIDE		SULPHATE AND BASE	SULPHATE CONVERTED TO BASE	SULPHATE AND BASE				SULPHATE CONVERTED TO BASE	

HISTORY AS IT WILL AFFECT THE INCIDENCE IN EACH DATE-OF-ENTRY GROUP :—

1950	1945	1940	1935	1930	1925	1920	1915
HYDROCHLORIDE	SULPHATE AND BASE HYDROCHLORIDE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE AND BASE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE CONVERTED TO BASE	

CHANGES INTRODUCED THAT WILL AFFECT EACH DATE-OF-ENTRY GROUP :—

1950	1945	1940	1935	1930	1925	1920	1915
	ISOLATION OF HYDROCHLORIDE	DISUSE OF SULPHATE CONVERTED TO BASE	RE-USE OF SULPHATE CONVERTED TO BASE	DISUSE OF SULPHATE CONVERTED TO BASE	ISOLATION OF BASE		

NO. OF CASES FOUND IN EACH PERIOD AS % OF NO. OF CASES EXPECTED IF RISK HAD REMAINED CONSTANT AT THE MEAN RISK :—

1950	1945	1940	1935	1930	1925	1920	1915
	300·0	78·1	20·4	180·0	153·8	73·1	
COMBINED POST-1935 106·6							

DATE-OF-ENTRY GROUP

FIG. 11.—The possible effect of the history of benzidine manufacture on the severity of incidence at different times.

Total Expected Number of Cases from the Nominal Roll in Group I Only

The type of graph shown to fit the observed incidences of bladder tumour in the various classes (see Figs. 9 and 10) makes it possible to calculate the numbers of cases that will be expected to occur on the assumptions that the death rate from other causes remains at the 1931 level, that none of the men on the nominal roll received further exposure after the end of 1950, and that the cases occur at the mean risk for the pre-and post-1930 periods for the men who entered at these times. By assuming in this way that conditions have remained static, it is practicable to obtain an indication of the number of cases which may still be expected in the population here considered, but since conditions have not in fact remained static the figures obtained are only a rough measure of the problems to be faced. They are shown in Table 8.

TABLE 8

NUMBER OF CASES EXPECTED FROM GROUP I

Exposure Class	Total No. of Cases Expected	No. of Cases Already Found	Further Cases to be Expected
Benzidine	58	34	24
α-Naphthylamine ..	70	19	51
β-Naphthylamine ..	93	55	38
Mixed exposures ..	265	135	130
Total	486	243	243

Another Measure of the Severities of the Risks in Each Exposure Class and in the General Population

In considering the risk involved in exposure to the three substances benzidine, α-naphthylamine, and β-naphthylamine, only patients who were dead, and where death certificates mentioning bladder tumour had been issued, could be used in determining the risk. It is now possible to devise another measure which will utilize the information from all the cases on the Group I nominal roll. This measure is the final incidence, after allowing for deaths from all causes at the 1931 rate, that will be reached for each class of exposure, and the comparison is with the final incidence for the general population. This can be calculated from the final incidence of death certification with mention of bladder tumour, together with the percentage certification with mention of bladder tumour of the cases in the hospital survey. The final incidence of death certification with mention of bladder tumour used is the figure for 1931 (0·56%) for men entering at age 34, this being the average age of entry for the period investigated. From this we find that the final incidence of cases of bladder tumour in the male general population is 0·70%, while the final incidences for benzidine, α-naphthylamine, β-naphthylamine, and mixed exposures in Group I are 13%, 11%, 43%, and 23% respectively.

This confirms the previous test and further provides a rough estimate of the severity of the hazard, the benzidine hazard being 19 times, the α-naphthylamine hazard 16 times, the β-naphthylamine 61 times, and the hazard from mixed exposures 33 times as great as that in the general population. In addition to the increased number of cases found, the occupational cases occur at a much earlier age than the non-occupational ones.

The Severity of the Risk in Groups II and III Firms

From the foregoing it is possible to calculate the number of cases that would have been expected from the nominal rolls of Group II and Group III firms if the risk were the same as in Group I, and to compare this expectation with the number of cases found whose names appear on the nominal rolls as having had contact with benzidine, α-naphthylamine, or β-naphthylamine. These figures are shown in Table 9. Both Group II and Group III firms have a lesser risk than Group I firms but the risk in Group III firms is not as small as was suggested by the figures derived from death certificates only.

TABLE 9

SEVERITY OF RISK IN GROUPS II AND III FIRMS COMPARED WITH RISK IN GROUP I FIRMS

Group under Consideration	No. of Cases Expected	No. of Cases Found	Potency of Risk as % of Group I Risk
Group II	48·7	7	14·4
Group III	4·1	2	48·7
Groups II and III combined	52·8	9	17·0

These figures also offer an additional means of testing the hypothesis that the mean induction time is not dependent on the severity of exposure. If it were, the mean induction time for these nine mixed exposure cases in the combined two groups should be longer than for the mixed exposure cases in Group I, and longer than the α-naphthylamine cases also. In fact, the mean induction time (21 S.D. 9 years) is not materially different from that of mixed exposure cases in Group I (18·3 S.D. 7. $P = 0·25$), and is shorter, though not materially so, than that of the α-naphthylamine cases from Group I firms (22·5 S.D. 7. $P = 0·55$).

A Possible Bladder Tumour Hazard in Other Dyestuffs Processes

It is now necessary to devote some attention to the cases that were found outside the groups which come into contact with benzidine or the naphthylamines. It has already been shown that aniline does not appear to present a hazard, but that the manufacture of magenta (fuchsine) appears suspicious.

The manufacture of auramine is also under suspicion. Four cases have appeared in auramine workers who have not had contact with either aniline, benzidine, or the naphthylamines, and two cases whose only contact with these substances has been with aniline. Nine other cases had worked on the manufacture of auramine, but also had contact with benzidine, α-naphthylamine, or β-naphthylamine. These nine cases were included in their appropriate exposure classes for the last three substances.

Two of the six auramine cases without such contact are still alive and three have bladder tumour death certificates. While it is impossible to say whether this figure represents an excess of cases over what might be expected if no occupational risk were present, unless the size of the population at risk is known, three death certificates seem highly suspicious when it is remembered that the total expectation from the 4,622 men on the combined nominal roll for aniline, benzidine, and α- and β-naphthylamine lay between three and five.

Fifteen cases amongst employees of member firms were found who were known not to have had contact with aniline, magenta, auramine, benzidine, or the naphthylamines. Seven of these have bladder tumour death certificates. The processes worked are shown in Table 10. These numbers are too small to allow a comparison between the age of onset and the age at death with those of the general population to be made, but there is no trend observable in this table to suggest that any of the processes listed there are to be suspected, but it is perhaps relevant to note that Henry, Kennaway, and Kennaway (1931) considered that occupations involving exposure to coal-gas, tar, pitch, or soot carried a risk of occupational tumour of the bladder. Two of the cases listed would fall into this category of worker, rather than into occupations proper to the chemical industry.

There are in addition 36 cases amongst past employees of member firms not participating in the scheme where it has been established that the men never had contact with aniline, auramine, benzidine, α- or β-naphthylamine, and of these, 34 have death certificates of tumour of the bladder. The seven cases with death certificates of tumour of the bladder from the previous group (Table 10) who had not had contact with benzidine or β-naphthylamine were combined with this group of 34, and their ages at death compared with the ages at death in the general population are shown in Fig. 12.

This figure shows that there is a movement towards the younger age groups and the statistical calculations show that, when allowance has been made for the fact that deaths at over the age of 65 may be missing from the chemical workers series because the death certificate might give the occupation as " retired, previous occupation unknown ", the shift is still real and is more than could reasonably be caused by chance sampling errors.

Thus, although it is impossible to say whether or not more tumours have occurred amongst chemical workers who have not had contact with aniline,

TABLE 10

PROCESSES WORKED BY CASES AMONG EMPLOYEES OF MEMBER FIRMS WITHOUT CONTACT WITH ANILINE, MAGENTA, AURAMINE, BENZIDINE, OR NAPHTHYLAMINES

Age at Onset	Age at Death	Processes	Length of Service
61	61. Died of other causes	Dinitrobenzene and dinitrotoluene	8 years
?	57	Diphenylamine, phenyl-peri-acid, primuline, sulphur colours, phenyl-beta-naphthylamine, o-nitro-aniline	25 years
66	67	Nitric acid manufacture	22 years
?	59	Picric acid manufacture	27 years
46	48	Manufacture of alizarine derivatives	28 years
?	74	Producer gas, handling tar and pitch Ice plant	5 years 1 year
50	53	Manufacture of sulphuric acid	2 years
?	48	Manufacture of dinitrophenol	5 years
53	Alive	Di-β-chloroethyl ether mono- and di-nitrations	7 years
59	Alive	Sodium hydrosulphite	1 year
47	Alive	Manufacture of amido-salicylic acid but worked in the same shed as a dianisidine plant	5 years
42	Alive	Para-, ortho- and chloro-para-toluidine. Next to sodium naphthionate plant	23 years
60	Alive	Use of acetic acid and acetic anhydride	2 years
74	Alive	Coal gas worker	3 years
		Chemical occupation not stated, but contact with any suspected chemical denied	46 years
57	Alive	Chemical occupation not stated, but contact with any suspected substance denied. However, his work was in a benzidine shed.	18 years

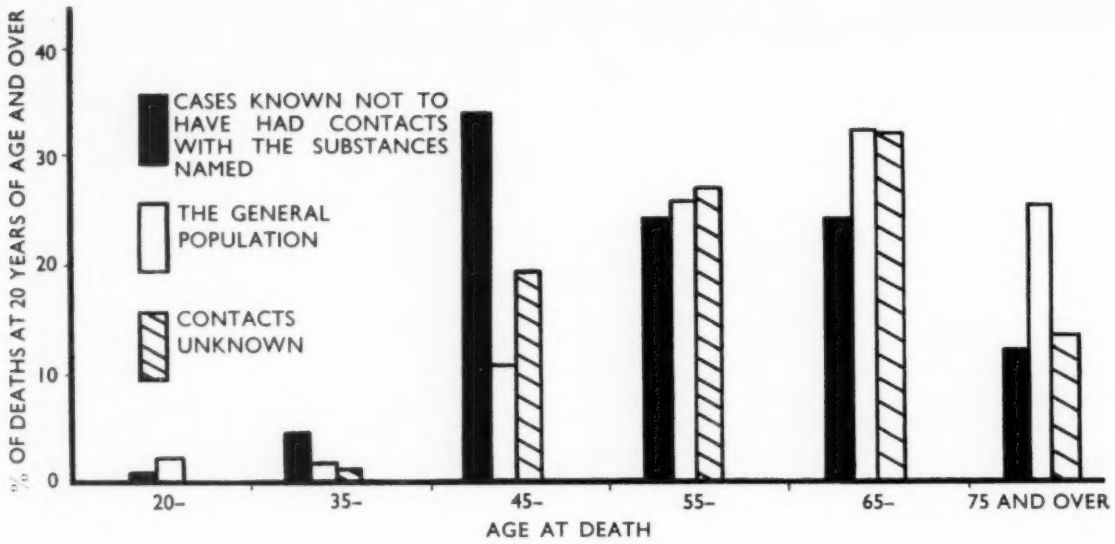

FIG. 12.—The age-distribution at death in 41 cases known not to have had contact with aniline, benzidine, α-naphthylamine, or β-naphthylamine, 81 cases with unknown contacts, and in the general population.

auramine, benzidine, α-naphthylamine, or β-naphthylamine than would be expected if they contracted the disease at the average rate for the general population, it is possible to say that the deaths occurred from bladder tumour at an earlier age than would be expected. This suggests that an environmental risk is operating in this group, but there is no evidence of the causes of the risk.

There now remains for consideration a group of cases whose contacts are unknown. These include 65 men whose employers are unknown, 10 men employed by firms no longer existing, three men employed by firms not members of A.B.C.M., and 11 men amongst the cases from participating firms. Of these 89 cases, 81 have death certificates mentioning tumour of the bladder.

The age distribution at death of these 81 cases is also shown in Fig. 12. Again there is a very slight movement towards the younger age groups, but this is no greater than could reasonably be attributed to chance sampling fluctuations, allowing for the possible loss of cases aged over 65 because of retirement. It is not possible to say whether or not an environmental risk is at work amongst this group.

Discussion

In general, each result has been discussed as it was achieved. Therefore no further discussion of the foregoing is needed. Certain general topics are however raised, and these are dealt with below.

It does not fall within the scope of this report to suggest alterations in industrial practice. However, it might not be out of place to make some suggestions for future investigation of the risk, so that changes due to better industrial practice can be assessed at an early date.

First, it is apparent that an accurate picture of what is happening can be obtained only from a study of both the population at risk and the cases derived from this population. Therefore it is important that accurate records of men employed should be kept, and their age, date of starting work, and occupational history noted. It would be desirable if records of causes of death of employees or past employees were also kept. It would then be possible for a firm concerned to make an estimate of the number of cases that might occur by the ordinary risk of the disease and the observed number, and so see what processes came under suspicion. The methods for doing this are set out and discussed elsewhere (Case, 1953b) and could be used by either the medical officer or the personnel management department.

Secondly, the number of cases that may be expected in the future makes early diagnosis important. The work of Crabbe (1952) using exfoliative cytology suggests that this method appears to offer advantages over older techniques. It might therefore be advisable to consider how far such a method could be applied in the dyestuffs industry generally.

Thirdly, it would seem desirable at this stage to

emphasize the need for more experimental work. If trace substances in intermediates play any part in the production of tumours, a possibility suggested by Case and Pearson (1952) and the unpublished work of Case (1948–52), quite different protective measures may be needed from those that would be required to prevent contact with the intermediates themselves. A prerequisite of protection is a knowledge of the forces against which protection is required.

Summary and Conclusions

This statistical survey demonstrates that contact with benzidine, α-naphthylamine, and β-naphthylamine in either manufacture or use causes many more bladder tumours in workmen so exposed than would appear if no special risk was operating. Furthermore, both the onset of and death from these occupational tumours takes place at a much earlier age than in non-occupational cases.

There is no evidence that aniline causes an increased number of bladder tumours in men who manufacture or handle it. There is, however, some evidence to suggest that the manufacture of magenta and auramine may cause tumours, and further details will be published in this journal later.

There is some evidence that work in the chemical industry which does not involve contact with any of these substances may cause earlier deaths from bladder tumour than occur in the general population, although figures are not available to measure whether a greater number of tumours is produced than would occur in the general population.

β-Naphthylamine has been the most potent cause of occupational bladder tumours between 1915 and 1951. In those firms which manufacture aniline, benzidine, α-naphthylamine or β-naphthylamine, the ratios of the potencies of β-naphthylamine, mixed exposures, benzidine, and α-naphthylamine in manufacture or use have been respectively 5·2, 2·7, 1·7, 1·0. However, when all the cases expected from this group have appeared, this ratio should change to 3·8, 2·0, 1·2, 1·0. This difference of ratio is due to the different times required for the tumours to become manifest.

The tumours appear after an induction period of an average length of 16 years for β-naphthylamine and benzidine and 22 years for α-naphthylamine. However, tumours may appear in less than two years from the first exposure or after more than 45 years from first exposure. Thus the length of time between the first exposure and the development of a tumour should not be considered as a bar to recognizing the tumour as being of industrial origin.

The average induction time is not appreciably influenced by the severity or duration of the exposure. It therefore appears to be a characteristic of the causal agent. This suggests that it is possible that the β-naphthylamine content of α-naphthylamine is not the sole causative agent in the latter substance unless it is assumed that α-naphthylamine could retard the production of β-naphthylamine tumours.

In the largest group available for study, that is the group of firms which manufacture aniline, benzidine, and either α- or β-naphthylamine, the final proportion of all workers employed for more than six months who had any contact, in the manufacture or use, with the latter three of these substances was about 20%.

Calculations suggest that, in the absence of any further exposure after 1951, this group of 2,466 men, which has already given rise to 243 cases, may be expected to produce a further 243 cases, making 486 cases in all. This calculation indicates only an approximate expectation, since many relevant conditions may be expected to have altered.

In other words, in this section of the chemical industry (Group I) one in 10 of the men exposed in the way defined above between 1915 and 1950 has already developed bladder tumour, and this figure may be expected to reach one in five before all the men are dead from all causes. The severity of the risk seems to have been mitigated slightly for men employed since 1930, and the data suggest that this comes from a diminution of risk in persons exposed to benzidine and mixed exposures. However, the risk is still such that taking the average post-1930 values, one in six of all men employed in contact with any of these substances may be expected to develop a tumour, whereas before 1930, one in four would be expected to do so. Since these data were collected, the manufacture of β-naphthylamine has been abandoned in Great Britain, and major alterations in techniques of manufacture and handling of α-naphthylamine have been introduced.

The actual risk of developing a tumour is influenced to a small extent by the age at which a man starts work in a hazardous occupation, there being a slightly increased susceptibility in older men. For all practical purposes, however, the age at which he is likely to develop a tumour, if he does so, is almost entirely dependent on the age at which he starts, being on the average 18 years later.

The length of exposure to a hazardous environment affects the chances of a man developing a tumour, but exposures of less than one year to β-naphthylamine, benzidine, or mixed exposures carry a definite risk. α-Naphthylamine requires a

longer exposure to produce an equivalent effect but too much reliance should not be placed on the absence of any cases with under one year's exposure, since the number of cases that could be expected if a risk is present is very small.

The use of sulphates or hydrochlorides instead of bases does not remove the risk, but there is evidence to suggest that the manufacture of benzidine sulphate followed by conversion to the base may be less hazardous than the direct isolation of the base.

STATISTICAL APPENDIX

THE COMPLETENESS OF DEATH CERTIFICATION AS BLADDER TUMOUR IN CASES SO DIAGNOSED IN A SAMPLE OF THE GENERAL POPULATION

Eight hundred and nineteen male patients with bladder tumour notified to us by the cooperating hospitals were found to have died between the years 1936 and 1949.

A complete alphabetical record of all death certificates mentioning tumour of the bladder for all males in England and Wales has been compiled for these years and this enables the certification to be checked. From these data Table Ia was computed.

TABLE Ia

COMPLETENESS OF DEATH CERTIFICATION MENTIONING BLADDER TUMOUR IN HOSPITAL SURVEY DATA

Nature of Tumour	No. of Cases	No. of Cases where Death Certificate Mentions Bladder Tumour	No. of Cases where Death Certificate does not Mention Bladder Tumour
Papilloma or benign tumour of bladder ..	103	47 (45·6%)	56 (54·4%)
Carcinoma of bladder ..	716	619 (86·4%)	97 (13·6%)
Total	819	666 (81·3%)	153 (18·7%)

Preparation and Analysis of the Nominal Roll

Twenty-one firms had provided nominal rolls. In most cases records were obtained from about 1920 onwards. This meant that many men whose names were on the nominal roll were employed before 1920 but were still in employment. If the date of first employment was before 1910 the names were discarded.

The names for each of the three groups of firms were allocated into date-of-entry groups, subdivided into these groups, 1910–1919, 1920–1924, 1925–1929, and so on to 1945–1949. For computing purposes these men were regarded as having started work in 1915, 1922·5, 1927·5, and so on in five-year intervals until 1947·5.

All the names of men which had been placed on the nominal roll, where the men had been employed by the firm for less than six months, were discarded. Some firms included women's names in the nominal roll, but since the numbers were few, and since death certificates for females were not available, these were not considered in this analysis.

Three firms submitted nominal rolls where information about dates of employment and age were omitted. The numbers concerned, and the groups affected, were as follows: Manufacture of aniline without magenta contact, 142 men between 1929 and 1950; mixed exposure, Group I, 44 men between 1915 and 1950; mixed exposure, Group II, 140 men between 1924 and 1950. These were allocated as described later.

The men in each date-of-entry group were further subdivided according to their age at entry, using the groupings under 20, 20–29, 30–39, 40–49, 50–59, 60 and over, and age unknown. The lay-out by cells of this type of subdivision is shown in the methods discussed by Case (1953b).

The men whose date of entry was unknown were now allocated to the classification age unknown for each age group in the period covered by the nominal roll of that firm. The allocation to each age group was made by taking the total number of men whose date of entry was known who entered the exposure class concerned after the date of beginning for the unknowns, and finding the percentage entering for each date-of-entry group subsequent to this date. This proportion of the unknowns was allocated to the appropriate age groups.

It had been noted that the distribution of numbers entering in each exposure group was fairly constant for that group from firm to firm, and probably reflected the economic structure of the industry at that date.

The expectation of death certificates mentioning tumour of the bladder, on the hypothesis that these accrue at the mean rate for England and Wales, can now be calculated from the equations described by Case (1953a). The steps used are discussed in detail by Case (1953b). The results of these calculations have been shown in Table 2 (p. 80).

In Group I, the group used for the critical evaluation of the existence of a hazard, the column " % of expected number derived from incomplete data " is put in to show that part of the expectation was calculated from the men who were allotted to the particular cells by the adjustment already described.

The probabilities are in all cases calculated from the estimate by the use of tables of the Poisson distribution. Where the probability value is on the border-line of

significance, the expectation derived from incomplete data should be considered in allotting a limit of significance. Thus the " all aniline " probability is not considered significant, only suspicious. The interpretation placed on the Table has been discussed in the report.

Effect of Age of Entry on Incidence of Bladder Tumour

It is convenient to consider this calculation here, since it is made from the nominal roll subdivided as just described. The analysis makes the assumption that entrants at each age of entry were distributed in equal proportions in each exposure class. This approximation involves only negligible errors. The numbers in each age-of-entry-cell are loaded with the appropriate constants from the 1931 life tables, and the expectation calculated from the observed crude percentage incidence (*vide infra*) for the pooled data (Table 4).

The mortality loaded figures show that there is an increased incidence in older persons but, since the numbers dealt with are so small, weighting constants for the increased incidence cannot be calculated with sufficient accuracy to be of value. Therefore, for the purposes of this analysis, the assumption will be made that the age of entry has no effect on the incidence of bladder tumour and this unjustified assumption will call for caution in the interpretation of the apparent reduction of risk after 1930, which will become overestimated.

Ages at Death and at Onset in General Population and in Different Categories of Chemical Workers

If a comparison between the age at death or onset in the chemical worker groups is to be made with similar data for samples representing the general population, it is necessary either to assume that the age-structure of the population at risk is sufficiently similar to the general population to prevent errors of a magnitude that would invalidate the conclusions or to have a sufficiently detailed knowledge of the population at risk to correct the figures to allow for the difference. In the instances under consideration, the former method is available for all categories of chemical workers, with the reservations to be discussed, and the latter method only in the case of death certificates derived from the nominal roll.

The age distribution of chemical and dyestuffs workers in England and Wales is set out in the Census returns (General Register Office, 1924 and 1934) for 1921 and 1931 and for Great Britain in the One per cent Census Sample (General Register Office, 1952), and these distributions are very similar to the age distribution of all males for the corresponding years. There is no reason for assuming that the dyestuffs division of the chemical industry has a widely different age composition from the broader classification of chemical and dyestuffs worker. The nominal roll itself defines a population at risk which would have a deficiency of older members, but the whole distribution is restored to that of the general population by the inclusion of those people who entered employment before 1910 and who are therefore ignored in the nominal roll.

If, therefore, we take all death certificates found (or all cases found where this is relevant) irrespective of whether they appear on the nominal roll or not, we are sampling from a population at risk similar in age composition to the general population, subject to a limitation that the sample is restricted to ages under 65, since owing to retirement and a stated occupation of " retired, previous occupation unknown " a bias will be introduced in older age-groups.

Where age of onset has been considered, the sample of the general population used is the Birmingham area. The population of this area is similar in age composition to the population of England and Wales (Padley, 1951).

The complete distribution for deaths in England and Wales for 1921–23, 1930–32 and 1946–49 compounded, for age at onset for Birmingham cases 1936–49, and for the various categories of chemical workers are shown in Table IIa. Table IIa also shows the curtailed distributions employed in the comparisons, obviating the bias discussed above.

In the case of the deaths derived from the nominal roll it is possible, by a series of partial summations of the comparative composite cohort analysis (Case 1953a, b) sum already used to obtain the total expected number, to calculate the exact expected distribution for the population shown in the nominal roll. This expected distribution is also shown in Table IIa, and is not affected by the bias discussed above.

The Induction Time

The grouped induction times for the Group I cases for each class of exposure, with the mean and standard deviation and the number of cases expected in each group for the pooled data if the distribution for the pooled data is a normal distribution are shown in Table IIIa.

Fig. 4 shows the frequency histogram of the pooled data fitted with the normal curve calculated for the appropriate mean and standard deviation. The distribution for the pooled data is shown to be normal, and a normal distribution around the respective means is assumed for the component exposure classes. Since the parent distribution is normal, and the distribution in each class approximates to normality, the significance of the difference of the means can be assessed by the use of the t test (Student, 1908). The values of t and the corresponding probability figures for the various differences of the means are also given in Table IIIa.

Influence of Severity of Exposure on Induction Times as Measured by Length of Exposure

There are 281 cases in Group I where both the exposure time and the induction time are known. These have been divided up by exposure time and induction time groups in Table 5. These data may be regarded as consisting of sub-classes, each independent, and each of which should conform to the appropriate segment of the parent normal distribution of induction time if this is independent of the exposure time.

The sub-classes are (1) all the cases where the induction times and the exposure times are co-extensive, to which must be added the 12 cases with exposure time of 20 to

TABLE IIa

AGE AT DEATH AND AGE AT ONSET FOR DATA AS SPECIFIED

Rank	Source of Data	Age Group													Total	Mean and S.D.	Distribution	χ^2 Analysis
		20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80 and over				
1	Death certificates for Males in England and Wales, 1920–1923, 1930–1932, 1946–1949	57			108	307	626	1086	1683	2482	2931	2845	2231	1516	15785	66·7 ± 9·4	Normal	—
2	All bladder tumour death certificates. Group I	5			7	15	23	27	21	10	18	7	2	2	137	—	Bimodal	$\chi^2 = 89{\cdot}8$ $n = 4$ $P < {\cdot}001$
	Curtailed expected number calculated from Rank 1	8·0					10·7	18·5	28·6	42·2	—				—	—	—	
3	Death certificates from nominal roll of Group I	0		13		41		36		21		6			117	—	—	$\chi^2 = 319{\cdot}0$ $n = 3$ $P < {\cdot}001$
	Expectation from cohort analysis	7·5						35·2		45·1		29·2			117	—	—	
4	Death certificates of cases known not to have had contact with aniline, benzidine, α- or β-naphthylamine ..	0				2	5	9	5	5	5	5	4	1	41	—	—	$\chi^2 = 8{\cdot}7$ $n = 2$ $P = {\cdot}015$
	Curtailed expectation calculated from Rank 1 ..	9·0							6·9	10·2	—				—	—	—	
5	Age at onset of 750 cases from Birmingham hospitals	1	8	9	21	29	43	93	110	128	132	92	54	30	750	61·4 ± 12·1	Approximately normal	—
6	Age at onset of all Group I cases where this was known	5		41		98		88		35	3	10			280	—	—	$\chi^2 = 129{\cdot}6$ $n = 4$ $P < {\cdot}001$
	Curtailed expectation calculated from Rank 5 ..	4·9		18·2		43·6		122·9		77·5	—				—	—	—	

30 years and induction time of over 30 years, since this figure is subject to a constraint which compels it to belong to this sub-class; (2) the complete row of data for each exposure time group excepting the cases mentioned above. These sub-classes all have an induction time in excess of the exposure time and, by definition, no case can have an exposure time greater than the induction time.

The expected numbers are calculated from the appropriate segments of the normal curve (m = 17·80 S.D. 7·18) of induction times, assuming a mean age of entry of 34 and adjusting the figures for loss through death from all causes by the English Life Table No. 10 for 1931 (Registrar General, 1945). The difference of the expectation from the observed numbers is assessed by the χ^2 technique, using Yates (1934) corrections for continuity where each sub-class has only one degree of freedom. The χ^2 is then summed over the whole, and no significant difference is found, and no trend for short exposures to give rise to long induction times is observed. In only one sub-class does the P value fall below 0·05.

The total expected distribution can then be found by summation (bottom line of table) and this also does not differ significantly from the total observed distribution.

Severity of Incidence of the Disorder in Population at Risk at Different Times

It is now necessary to study the dynamics of the rate of appearance of cases of bladder tumour by relating the cases to the population at risk from which they were derived. The best sample of the population at risk which is available is the nominal roll. Not all of the cases previously discussed appear on the nominal roll. Some were diagnosed before adequate records were kept, and some were men who had, for various reasons, been omitted from the nominal roll. The allocation of such cases to the nominal roll would cause a bias. Therefore a case of bladder tumour was considered as derived from the nominal roll only if the man's name appeared on the nominal roll as supplied. All other cases are omitted from the following calculations.

The number of men on the nominal roll, and the number of cases derived therefrom for Group I are

TABLE IIIa

DATA RELATING TO THE INDUCTION TIME OF GROUP I CASES

Induction Time in Years	Number of Cases by Exposure Class					Total Cases Expected if Distribution is Normal
	Benzidine	α-Naphthylamine	β-Naphthylamine	Mixed Exposures	Pooled Data	
0–	0	2	2	1	5	8·6
5–	6	0	9	12	27	29·5
10–	10	0	17	45	72	62·0
15–	12	7	16	45	80	79·4
20–	9	8	11	31	59	62·0
25–	1	3	4	15	23	29·5
30–	0	2	0	9	11	
35–	0	1	0	1	2	
40–	0	0	0	0	0	10·1
45 and over	0	1	0	1	2	
					15	
Unknown ..	0	2	0	3	5	—
Total	38	24+2	59	160+3	281+5	281·1
Mean	16·05	22·46	15·64	18·32	17·80	χ^2 = 7·3
S.D.	5·45	6·23	6·22	7·11	7·18	n = 6
Coefficient of variation	34·0%	27·7%	40·0%	38·8%	40·3%	P = ·3
Exposure Class						
Benzidine	—	t = 4·29 P < ·001	t = 0·33 P = ·6	t = 1·84 P = ·055	t = 1·62 P = ·1	Significance of difference of means by t test
α-naphthylamine..	—	—	t = 4·50 P < ·001	t = 2·69 P = ·008	t = 3·56 P < .001	
β-naphthylamine..	—	—	—	t = 2·55 P = ·015	t = 2·63 P = ·012	
Mixed	—	—	—	—	t = 1·38 P = ·15	
					Pooled data minus class under consideration	

The dotted line indicates groups combined together in carrying out χ^2 test.

TABLE IV

ADJUSTED NOMINAL ROLL OF GROUP I BY EXPOSURE CLASS AND

Exposure Class	Date of Entry											
	1915				1922·5				1927·5			
Aniline without magenta contact	2	0	1	3	4	6	2 *1**	5	1	2	2 *1**	7 *1*
	13		1	20	33		2	52 *1**	13		4	29 *2**
Aniline with possible magenta contact	0	0	3	3	5	9	8 *1*	3 *1*	0	3 *1*	3	4 *1*
	6		2	14	43		0	68 *2*	42			52 *2*
Benzidine	13	16 *1*	1	2 *2*	33 *1*	7 *2*	1 *1*	8 *4*	6	1 *1*	0	17 *9*
	10		1	43 *3*	67 *2*		0	116 *10*	36 *1*		0	60 *11*
	6·98				8·62				18·33			
β-Naphthylamine	4	6 *1*	2 *2*	6 *4*	4 *1*	4 *3*	11 *3*	4 *4*	7	42 *9*	3 *3*	6 *6*
	5 *1*		0	23 *8*	1 *1*		0	24 *12*	8		0	66 *18*
	34·78				50·00				27·27			
α-Naphthylamine	9	52	17	5 *3*	17	14	1 *1*	6 *2*	1	10	0	7 *3*
	4 *1*		1 *1*	88 *5*	13 *1*		0	51 *4*	16 *1*		0	34 *4*
	5·68				7·84				11·76			
Mixed exposures	1 *1*	5 *3*	9 *9*	43 *13*	5	20 *7*	15 *4*	38 *13*	7 *1*	43 *8*	21 *12*	52 *16*
	62 *7*		5	125 *33*	57 *6*		5	140 *30*	65 *2*		11	199 *35*
	26·40				21·43				19·09			
Benzidine, α-naphthylamine, β-naphthylamine, and mixed exposures	27 *1*	79 *5*	29 *11*	56 *22*	59 *2*	45 *12*	28 *9*	56 *23*	21 *1*	96 *18*	24 *15*	82 *30*
	81 *9*		7 *1*	279 *49*	138 *10*		5	331 *56*	125 *4*		11	359 *71*
	17·56				16·92				19·78			
Key to exposure time in years	<1	1–	5–	10–								
	20+		?	Total								

The figure in italics is the number of derived cases.

EXPOSURE TIME WITH DERIVED CASES AND CRUDE PERCENTAGE INCIDENCE

Date of Entry													Total			
1932-5				1937-5				1942-5				1947-5				
0	4 *1*	1	10	0	8	19	24	7	13	14	7	7	35	11	0	21	68 *1*	50 *2**	56 *1*
6		18	39 *1*	1		43	95	0		34	75	0		43	96	66		145	406 *4**
0	1	0	15 *1*	0	3	3	13	0	7	12	14	0	104	14	0	5	127 *1*	43 *1*	52 *3*
5		1	22 *1*	0		0	19	0		0	33	0		0	118	96		3	326 *5*
3	8	10	31 *2*	15	24 *1*	18 *3*	30 *1*	4	22 *1*	11 *2*	15	10	40	25	0	84 *1*	118 *6*	66 *6*	103 *18*
11		0	63 *2*	0		0	87 *5*	0		0	52 *3*	0		0	75	124 *3*		1	496 *34*
3·17				5·75				5·77				0·00				Crude percentage incidence			
0	10 *2*	7 *7*	9 *1*	1 *1*	5 *1*	5 *2*	14 *2*	0	4 *1*	1	3	5	33	5	0	21 *2*	104 *17*	34 *17*	42 *17*
3		0	29 *10*	0		0	25 *6*	0		0	8 *1*	0		0	43	17 *2*		0	218 *55*
34·48				24·00				12·50				0·00				Crude percentage incidence			
12	20	12	24 *4*	1	15	13 *1*	40	0	26	15	13	20	152 *1*	64	0	60	289 *1*	122 *2*	95 *12*
8		0	76 *4*	1		0	70 *1*	0		0	54	0		0	236 *1*	42 *3*		1 *1*	609 *19*
5·26				1·43				0·00				0·42				Crude percentage incidence			
9	18 *1*	32 *3*	81 *17*	24	37 *2*	20 *2*	79 *4*	17	16	22 *1*	36 *3*	16 *1*	146	68	0	79 *3*	285 *21*	187 *31*	329 *65*
30		8	178 *21*	1		6	167 *8*	0		4	95 *4*	0		9	239 *1*	215 *15*		48	1143 *135*
11·80				4·79				4·21				0·42				Crude percentage incidence			
24	56 *3*	61 *10*	145 *24*	41 *1*	81 *4*	56 *8*	163 *7*	21	68 *2*	49 *3*	67 *3*	51 *1*	371 *1*	162	0	244 *6*	796 *45*	409 *56*	569 *112*
52		8	346 *37*	2		6	349 *20*	0		4	209 *8*	0		9	593 *2*	398 *23*		50 *1*	2466 *243*
10·69				5·73				5·83				0·34				Crude percentage incidence			

* Also exposed to the manufacture of auramine.

shown in Table IVa. The date of entry is grouped as previously described, and the exposure time into groups of under one year, between one and five years, between five and 10 years, between 10 and 20 years, over 20 years, and not known. The contribution from the last class is very small, being 1·6% for the nominal roll and one case (0·4%) for the other series.

The percentage incidence of bladder tumour that had been attained in each exposure class by February, 1952, can now be calculated from the total for each date-of-entry group. This figure, which makes no allowance for the length of exposure, is referred to as the crude percentage incidence, and is also shown for the exposure classes other than the two aniline classes.

Since the induction times are normally distributed and are uninfluenced by severity of exposure, these crude values should approximate to a cumulative sigmoid normal curve, unless the risk has altered during the years. The values and the calculated normal curve have been shown in Fig. 5. This curve is calculated from the mean and standard deviation of the pooled data and the total number of cases, and has a final incidence of 21%. The goodness of fit of this curve is tested by calculating the number of cases expected in each date-of-entry group. These figures are shown in Table Va.

The cumulative sigmoid normal curve is calculated by finding the regression equation of the probit of the percentage of the final incidence. This equation is derived as follows :

For cumulative sigmoid normal curve, 16% of the whole area lies to the left of the ordinate one standard deviation below the mean (m). The probit of 16% is 4·01. The probit at the mean is 5·0. The regression equation of a straight line, $Y = a + bX$ can then be found by $b = (5{\cdot}00 - 4{\cdot}01)/\sigma$

$a = 5{\cdot}00 - bm$

where Y = probit of percentage of final incidence

and X = time in years since entering exposure.

The regression equations for each class of exposure are thus :

Benzidine	$Y = 2{\cdot}08 + 0{\cdot}182X$
α-Naphthylamine	$Y = 1{\cdot}43 + 0{\cdot}159X$
β-Naphthylamine	$Y = 2{\cdot}51 + 0{\cdot}159X$
Mixed exposures	$Y = 2{\cdot}45 + 0{\cdot}139X$
Pooled data	$Y = 2{\cdot}56 + 0{\cdot}138X$

Effect of Length of Exposure

The effect of length of exposure was investigated as follows :

The crude incidences were calculated by assuming that all exposure times contributed an equal weight to the incidence. This weight may be termed the mean effective exposure. If the percentage number of men on the nominal roll who would have developed tumours at the crude percentage incidence for each date-of-entry group and each class of exposure is found, this may be compared with the number who actually did develop tumours. The summation of the expected number at the relevant crude percentage incidence over all date-of-entry groups for each length of exposure group, compared with a similar summation for the cases actually appearing, will give a measure of the effect of exposure time. This has been shown in Fig. 7.

Adjusting Curves to Remove Effects of Exposure for Different Times at Different Dates

The effective population at risk can now be calculated from the adjusted nominal roll and these weights for each exposure class. The theoretical percentage incidence is then calculated from this figure and from the number of cases actually found. The figures for the pooled data are then calculated as the sum of the component classes. These effective figures are given in Table VIa.

Measurement of Relative Potency of Each Exposure Class

The numbers in rank 5 of Table VIa represent a mean potency that may be used as an arbitrary standard by which to measure the potency of each component exposure class. The relative potency of each component exposure class may now be calculated by determining the number of cases that would be expected in that exposure class if the substance had the mean potency, summating over the whole exposure class, and comparing this figure with the number of cases actually found. The numbers expected as percentages of the numbers found are called the relative potencies, and have also been shown in Table 7.

Test of the Internal Consistency of these Data

These figures have been calculated by using mean figures for the effect of length of exposure, and from a summation over the date-of-entry groups. It is therefore necessary to see that fluctuations of temporal conditions do not invalidate the calculation, and accordingly a test was applied by calculating the numbers that would be expected for each date-of-entry class and each exposure

TABLE Va

NO. OF TUMOURS EXPECTED FROM CRUDE PERCENTAGE INCIDENCES FOR POOLED DATA IF OVERALL RISK REMAINS CONSTANT AND NO. FOUND CALCULATED FROM SIGMOID NORMAL CURVE FITTED TO MEAN INDUCTION TIME OF 17·8 ± 7·18 YEARS AND 243 CASES

Date of Entry	1915	1922·5	1927·5	1932·5	1937·5	1942·5	1947·5	Total	Difference of Distribution
No. expected	57·8	63·8	56·7	37·5	19·2	4·2	2·9	242·1	$\chi^2 = 7{\cdot}1$
No. found..	49	56	71	37	20	8	2	243	n = 5 P = ·25

The dotted line indicates groups combined together in carrying out χ^2 test.

TABLE VIa

EFFECTIVE POPULATION AT RISK, NUMBER OF CASES FOUND, AND EFFECTIVE PERCENTAGE INCIDENCE

Exposure Class	Date of Entry							
	1915	1922·5	1927·5	1932·5	1937·5	1942·5	1947·5	
Benzidine	33·0	51·3	51·4	115·0	153·8	94·2	92·3	Effective population at risk
	3	10	11	2	5	3	0	Cases
	9·1	19·5	21·4	1·7	3·3	3·2	0·0	Percentage incidence
α-Naphthylamine ..	64·5	35·2	39·6	106·8	157·3	65·5	91·0	Effective population at risk
	5	4	4	4	1	0	1	Cases
	7·8	11·4	10·1	3·8	0·6	0·0	1·1	Percentage incidence
β-Naphthylamine ..	19·6	28·0	51·9	32·6	31·4	8·8	36·3	Effective population at risk
	8	12	18	10	6	1	0	Cases
	40·8	42·8	35·2	30·7	19·1	11·4	0·0	Percentage incidence
Mixed exposures ..	113·2	130·7	192·0	221·1	210·6	125·7	306·9	Effective population at risk
	33	30	38	21	8	4	1	Cases
	29·2	23·0	19·8	9·5	3·8	3·2	0·3	Percentage incidence
Pooled data	230·3	245·2	334·9	475·5	553·1	294·2	526·5	Effective population at risk
	49	56	71	37	20	8	2	Cases
	21·3	22·8	21·2	7·8	3·6	2·7	0·4	Percentage incidence

group from the expectation at mean potency multiplied by the relative potency factor, and comparing the distribution of the expectation with the number of cases actually found. The data were found to be internally consistent.

Effect of Temporal Conditions

The above test of internal consistency dealt only with possible variations of the ratio of potencies, and would not reveal an absolute diminution of potency if these ratios were maintained. Such an absolute diminution would be expected if improvements in technique in more recent years had been effective. This possibility was investigated as follows :

The number of cases expected from the effective population at risk, on the hypothesis that no alteration of risk has occurred, was calculated from the mean value of the appropriate segments of the cumulative sigmoid normal curve corresponding to the year-of-entry groups used. These estimates are weighted with values derived from the Life Tables for Males, England and Wales, 1931 (Registrar General, 1945). The year 1931 is chosen as being the life table most appropriate to the whole period 1915–1950.

These expectations, with the numbers actually found, are shown in Table VIIa.

The changes of conditions and techniques that might be expected to produce a diminution of risk began about 1935. However, the men entering in the group 1930–35 would be affected by these changes since it has been shown that the full effect of exposure is not developed until after more than five years' exposure. Accordingly, these data were considered in two groups, those entering before 1930, and those entering in or after this date. The table shows that there is an apparent diminution of risk in the exposure classes benzidine and mixed exposures, and in the pooled data, and the χ^2 test shows that this is significant. No significant change is found for β-naphthylamine or α-naphthylamine.

This test gives no idea of the magnitude of the reduction of risk, and this was evaluated in the following manner :

The two groups, pre-1930 and post-1930, were regarded

TABLE VIIa

CALCULATED NUMBER OF CASES FOR EACH EXPOSURE CLASS EXPECTED IF RISK HAS REMAINED CONSTANT AND NO. ACTUALLY FOUND

Exposure Class	1915	1922·5	1927·5	Total pre-1930	1932·5	1937·5	1942·5	1947·5	Total post-1930	Total		χ^2 Corrected for Continuity
Benzidine ..	4·2	6·4	6·1	16·7	9·7	6·4	1·1	0·1	17·3	34·0	Expected	5·441
	3	10	11	24	2	5	3	0	10	34	Found	P = ·02
α-Naphthylamine	7·6	3·5	2·7	13·8	3·6	1·5	0·1	0·0	5·2	19·0	Expected	0·023
	5	4	4	13	4	1	0	1	6	19	Found	P = ·85
β-Naphthylamine	8·3	11·6	19·7	39·6	9·4	5·1	0·5	0·4	15·4	55·0	Expected	0·110
	8	12	18	38	10	6	1	0	17	55	Found	P = ·75
Mixed exposures	25·7	28·4	35·2	89·3	27·9	13·5	2·7	1·6	45·7	135·0	Expected	4·140
	33	30	38	101	21	8	4	1	34	135	Found	P = ·04
Pooled data ..	45·8	49·9	63·7	159·4	50·6	26·5	4·4	2·1	83·6	243·0	Expected	4·730
	49	56	71	176	37	20	8	2	67	243	Found	P = ·03

as being segments of two sigmoid cumulative normal curves, weighted for mortality, the curves of each exposure class having the same characteristics but different final incidence figures. The final incidence for the post-1930 group expressed as a percentage of the final incidence of the pre-1930 group gives a measure of the change of risk since 1930. These calculations are shown in Table VIIIa. The significance is derived from

TABLE VIIIa
EVALUATION OF THE POST-1930 RISK

Exposure Class	Final Percentage Incidence Expected		Post-1930 Value as Percentage of pre-1930 Value	Significance
	Pre-1930	Post-1930		
Benzidine	21·53	8·59	40%	Yes
α-Naphthylamine ..	14·48	17·52	118%	No
β-Naphthylamine ..	47·43	56·01	118%	No
Mixed exposures ..	32·91	21·93	67%	Yes
Pooled data ..	30·26	19·94	66%	Yes

the χ^2 test previously shown in Table VIIa. There is an overall reduction of risk of about 34% and this is contributed to by a diminution of risk in the exposure classes benzidine and mixed exposures.

Number of Further Expected Cases in Group I

The additional cases that may be expected from the nominal roll of the Group I firms, on the assumption that no further contact takes place after 1950 and that the mortality from all causes remains as in 1931, are calculated from the effective populations at risk and the final percentage incidences for pre- or post-1930, according to when the men entered risk. These results have been shown in Table 8. The large number of α-naphthylamine cases expected suggests that the potency factors already calculated may have underestimated the potency of this material. They were calculated from cases that have already occurred, and a bias would be introduced because of the longer mean induction time of these cases.

Another method of estimating the relative potency is to calculate the ratios of the final incidences expected at standard (1931) mortality. This has accordingly been done by methods already described. These figures are termed the ultimate relative potencies. These results have been shown in Table 7. These values show that α-naphthylamine and mixed exposures have been undervalued, and benzidine and β-naphthylamine overvalued by the previous method.

Severity of Risk in Groups II and III Firms

The nominal rolls for Group II and Group III were adjusted and set out as described previously for date of entry and length of exposure. Since the numbers were small, only the pooled data were used. These figures were then corrected for length of exposure, using the factors derived from Group I firms. The expected number of cases was then calculated by multiplying these values by the final incidence (26·57%) for the pooled data for Group I and by the appropriate constant for the date of entry, and summating over all date-of-entry groups. The mean age of entry for Group II was 34, and for Group III was 23. The expectation for Group III was therefore adjusted by multiplying by the calculated factor 1·110 to adjust for this. The numbers actually found were expressed as a percentage of these figures to give an estimate of the overall risk in Groups II and III compared with Group I. The results of these calculations have been shown in Table 9.

It is a pleasure to pay tribute to the patience and industry of the member firms who have cooperated so well in the provision of detailed records. Many hospitals have also been of the utmost assistance, and our thanks are due to all these, to the General Register Office, and to the Factory Department of the Ministry of Labour. It is perhaps invidious to cite individuals from amongst all these willing helpers, but the report would not be complete without expressing a particular appreciation of the great help afforded by Dr. Denton Guest of the Huddersfield Royal Infirmary and Miss J. M. Levi of the Birmingham United Hospitals.

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TUMOURS OF THE URINARY BLADDER IN DOGS AFTER INGESTION OF 4-AMINODIPHENYL

BY

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4-Aminodiphenyl was discovered by Hofman in the residues of aniline manufacture in 1862, and yet it is only in recent years that it has come to be considered for use in the organic chemical industry in England. In 1950 it seemed to us that this amine might have been partly responsible for "aniline cancers" of the bladder amongst dyestuff workers in Germany before 1920 and that its manufacture and use at the present day, if undertaken without adequate precautions, would involve a hazard to those concerned. We therefore started an investigation into its carcinogenic potentialities in rats and dogs.

The results of our experiments with rats have already been published in this journal (1952). Tumours of the liver, intestine, and mammary gland were found following the repeated subcutaneous injection of 4-aminodiphenyl in arachis oil. The present paper describes the effects of feeding the amine to dogs.

Experimental Details

Two male Beagle litter-mates aged 7 months were used in the experiment. They were fed on minced raw meat and houndmeal, supplemented with vegetables, bone meal, salt and cod-liver oil, as were the rest of the pack. 4-Aminodiphenyl, (b.p. 302° C. at atmospheric pressure) was administered on a weight basis in capsules by mouth. The animals were dosed once daily, six days a week, and details were as follows :

Both animals gained weight during the experiment; dog 457 weighed 8·4 kg. at the start and rose to 13·2 kg. at death, whereas dog 458 gained 3·2 kg. from 10 kg. Poor appetite or loss of weight were used as indications either for the lowering of the dose level or for temporary cessation of dosing. On January 1, 1952, we considered that the results obtained in rats up to that time did not warrant the continuance of the experiment with dogs, and dosing was stopped. Then, on June 1, 1952, 18 months after the beginning of the experiment, dog 457 was noticed to have haematuria, which persisted for a month. Since dogs fed with benzidine in many laboratories have failed to develop tumours when observed over five years, we found it hard to believe that haematuria so early in our experiment was due to the presence of a tumour. However, dosing at 5 mg./kg. was begun again on June 30, 1952, and continued until February 10, 1953.

DOSES OF 4-AMINODIPHENYL

Dose Level (mg./kg.)	Time of Administration	Dog 457		Dog 458	
		Dose (g.)	Cumulative Total Dose (g.)	Dose (g.)	Cumulative Total Dose (g.)
20·0	27.11.50–7.1.51	4·80	4·80	6·00	5·00
10·0	8.1.51–27.2.51	3·42	8·22	4·46	10·46
7·5	28.2.51–28.3.51	1·57	9·79	1·44	11·90
5·0	29.3.51–31.12.51	10·43	20·22	10·95	22·85
Nil	1.1.52–29.6.52	Nil	20·22	Nil	22·85
5·0	30.6.52–10.2.53	10·04	30·26	10·71	33·56

Dog 457 had haematuria at intervals after November 5, 1952, but both dogs remained quite healthy, ate well, and maintained their weight until September, 1953, when dog 457 lost its appetite, had a series of fits and, after a few days, became unconscious. On the same day, dog 458 also became unconscious. A clinical diagnosis of terminal uraemia was made in each case and both dogs were killed on September 2, 1953, two years nine months after the start of oral dosing with 4-aminodiphenyl.

Post-mortem Examination

Dog 457 was well nourished, and there were no abnormal external appearances, except for much frothy saliva in the mouth. (There had been a generalized convulsion within a few minutes of death.)

The thoracic contents appeared normal, except for congestion of both lungs. There was no pericarditis and no serous effusions.

The stomach appeared normal as did the rest of the intestinal tract, except for a small quantity of blood in the lumen of the small gut.

The liver, spleen, pancreas, adrenals, kidneys, ureters, and prostate appeared normal. The brain was not examined.

The bladder was contracted and, on palpation, felt as if it were a solid organ. The surface appeared normal and no pelvic adhesions were present. On opening the organ a very small quantity of urine was released which was not bloodstained. The bladder lumen was nearly occluded by multiple epithelial tumours growing from the bladder wall. These tumours showed their greatest development in the dome of the bladder, and were relatively sparse at the base, where apparently normal mucosa could be seen between them. The tumours were grey ; some were pedunculated, but the majority were sessile.

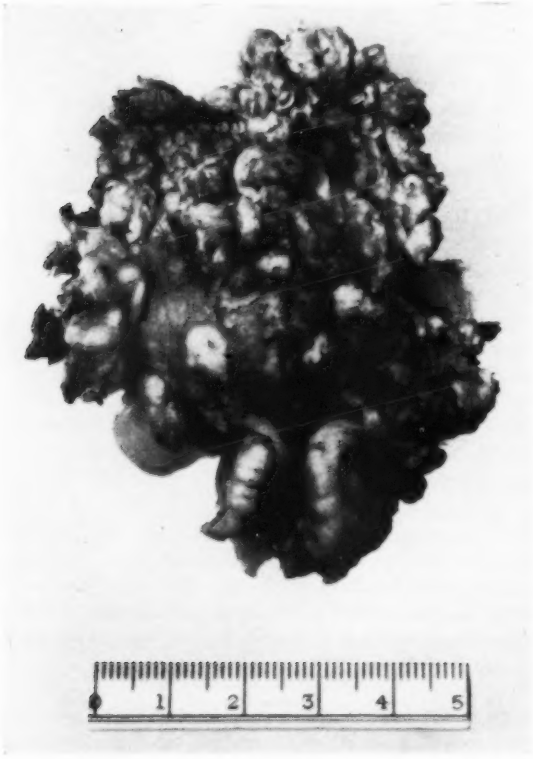

FIG. 1.—Mucosal surface of the bladder of dog 458, showing papillomatosis. The tumours are large and closely packed in the upper two-thirds of the organ, and relatively sparse in the lowest third. Natural size.

Dog 458 was well nourished and there were no abnormal external appearances.

The thoracic contents appeared normal ; there was no pericarditis and no serous effusions were present.

Submucous haemorrhages were present in the stomach and in the intestines, while the spleen and pancreas appeared normal. The liver was congested and fatty. The adrenals, ureters, and prostate appeared normal, while the kidneys were congested. The brain was not examined. The abnormal findings in the liver were confirmed by microscopy.

The bladder was globular in shape, contracted, and the wall thickened. The surface appeared normal and there were no pelvic adhesions. On opening the organ, approximately 10 ml. of urine were released, This was not bloodstained.

Multiple, closely packed tumours were present over the whole internal surface of the upper two-thirds of the organ, while in the lowest third the tumours were fewer, relatively large areas of apparently normal mucosa appearing between them The tumours were grey, most were pedunculated, but some were sessile.

The gross appearance of the organ is seen in Fig. 1.

Microscopic Examination of the Bladders.—The tumours were similar to those previously described by Bonser (1943), the bladder epithelium showing a graded series of changes from simple hyperplasia to infiltrating carcinoma.

The simplest change was a thickening of the epithelium together with some swelling of the cells. Microcysts caused, presumably, by degeneration of cells were frequent.

With increased thickening of the epithelium, a mass of cells either acquired a connective tissue core, becoming a pedunculated papilloma (Fig. 3), or formed an irregular sessile mass projecting into the lumen of the bladder. In some cases projections of epithelial cells passed down into the subjacent connective tissue (Fig. 4).

Larger growths, both simple and malignant, were also found. These were either transitional-cell tumours, anaplastic tumours showing much cellular pleomorphism (Fig. 5), or tumours composed of small cells with small, round, closely packed, deeply staining nuclei, a small amount of basophilic cytoplasm and indefinite cell boundaries. Mixed structure was common and tubule formation frequently seen (Fig. 6).

In dog 457 infiltration of the wall of the bladder by tumour cells was limited to the sub-epithelial connective tissue, stopping just short of the muscle

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 2.—Section of bladder of dog 457 with pedunculated papilloma in centre and more sessile growths on either side. × 4.

FIG. 3.—A very early papilloma in the bladder of dog 457. × 90.

FIG. 4.—Gross thickening of the epithelium of the bladder of dog 457 with microcyst formation. Groups of epithelial cells pass down into the subepithelial connective tissue. × 90.

FIG. 5.—Edge of an area of anaplastic carcinoma in the bladder of dog 457 × 90.

bundles, but in dog 458 there was deep infiltration, carcinoma cells being found deep in the musculature of the bladder wall but not reaching to the surface of the organ (Fig. 7).

Conclusions

The occurrence of bladder tumours in these two dogs, two years nine months after the start of dosing with 4-aminodiphenyl, is more significant if the records of the remainder of our Beagle pack are considered. Haematuria has never been observed. Thirty animals of the pack are now 3 to 9 years old and in six others over 3 years of age which have died from various causes and have been examined post mortem, no bladder tumours have been found.

Bladder tumours have been produced in dogs by feeding with β-naphthylamine, benzidine, 2-acetylaminofluorene, N : N-dimethyl-4-aminoazobenzene and 4-amino-3 : 2′-azotoluene. It is interesting to compare the appearance of such tumours in our two dogs after 33 months, when only 30 to 34 g. of 4-aminodiphenyl had been given, with the results obtained with these other amines. Spitz, Maguigan, and Dobriner (1950) and Spitz (personal communication) found that the three longest survivors of seven dogs given approximately 325 g. of benzidine by mouth developed papillomas and carcinomas of the bladder after 84, 96, and 120 months respectively. Morris and Eyestone (1953) obtained bladder tumours in four Beagles at 68–91 months with total doses of 90–198 g. of 2-acetylaminofluorene, but no tumour in another which was given only 45 g. of the amine and observed for 87 months. From Nelson and Woodard's paper (1953) it is not clear what total dose of N : N-dimethyl-4-aminoazobenzene and 4-amino-3 : 2-azotoluene these authors gave, but their four dogs with bladder tumours died after 30, 38, 43, and 48 months respectively. Hueper and Wolfe (1937), and Hueper, Wiley, and Wolfe (1938), with total doses of β-naphthylamine ranging from 58 to 130 g. obtained bladder tumours in a minimum time of 18 months. These lesions, however, were first detected by cystoscopy, and not until later was haematuria observed. It seems likely that tumours were already forming in the bladders of our dogs when haematuria was seen at 18 months. Bonser (1943), who obtained similar tumours in 44, 50, and 60 months in dogs given massive doses of β-naphthylamine, also observed haematuria some time before death. Gehrmann, Foulger, and Fleming (1949) have reported the production of a bladder tumour with 15 g. of β-naphthylamine, but this did not appear until some six and a half years after the start of dosing.

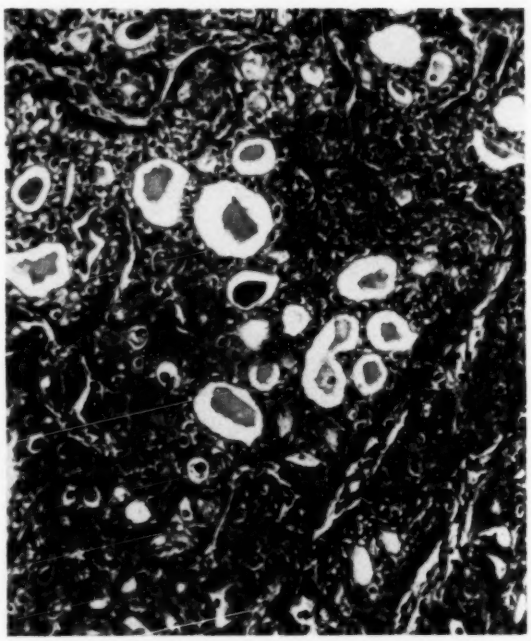

FIG. 6.—Tubule formation in a malignant papilloma of mixed structure in the bladder of dog 458. × 150.

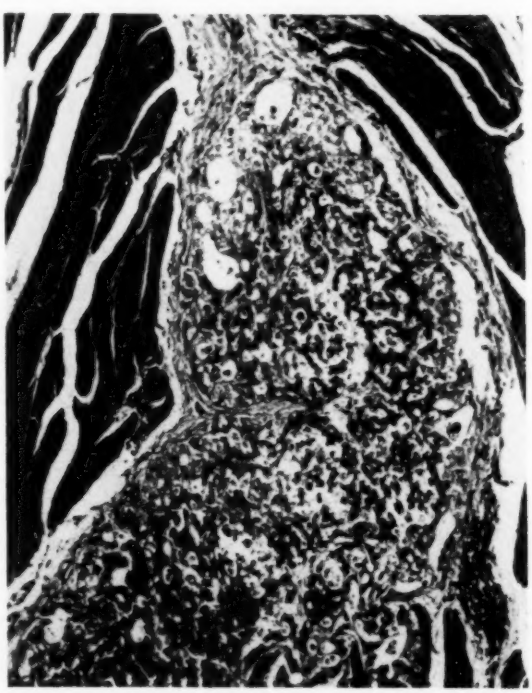

FIG. 7—Nodule of carcinoma cells deep in the musculature of the bladder of dog 458. × 90.

On balance, therefore, it would appear that 4-aminodiphenyl is at least as active as a bladder carcinogen in the dog as β-naphthylamine, and considerably more potent than benzidine or 2-acetylaminofluorene. Of the amines which have been shown to be active in this respect, only β-naphthylamine and benzidine have so far been manufactured on a large scale and both have been responsible for a high incidence of bladder cancer in the work people involved. Owing to the timely discovery by Wilson, De Eds, and Cox (1941) of the carcinogenic action of 2-acetylaminofluorene, this otherwise promising insecticide has not been manufactured commercially.

These considerations lend additional support to our suggestion in our carlier paper (*op. cit.*) that 4-aminodiphenyl played a part, together with β-naphthylamine and other high boiling aromatic amines, in the genesis of some of the bladder tumours in dyestuff workers which occurred in Germany during the early years of this century, and which have been attributed to aniline. We therefore conclude that its manufacture and handling today would carry with it grave risks to the working population involved unless adequate precautions were taken to avoid skin contact or the inhalation of vapour or dust by the use of totally enclosed plant and daily changes of clothing for the operatives.

Summary

After being given 4-aminodiphenyl by mouth in a total dose of 30 to 34 g. (2·9–3·3 g. per kg.) the two Beagle dogs in our experiment were killed when they had advanced bladder tumours, two years nine months after the start of dosing.

This amine appears to be more effective as a bladder carcinogen in the dog than either benzidine or 2-acetylaminofluorene, and at least as potent as β-naphthylamine.

It is concluded that this substance should not be manufactured or handled in the chemical industry without the most stringent precautions.

We wish to thank Mrs. A. B. Hallam for her help in dosing the animals.

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AN INDUSTRIAL HEALTH SERVICE IN NORWAY*

BY

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Norway has an area of approximately 320,000 square kilometres, with a population of only about 3·2 millions. About 30% of the population live in the cities, whereas 20% live in suburban and industrial areas and other population centres, and the remaining 50% in rural areas.

The main occupations in Norway are agriculture and forestry, fishing and whaling, manufacturing and trade, as well as business and transport. During the years preceding and following the last world war Norway has been increasingly industrialized. Thus, the census of 1946 revealed that those employed in manufacturing and trade constituted the largest occupational group, with a total of 480,000 persons, 80,000 of whom were women.

The most important industrial enterprises are the iron and metal industry, the food industry, the pulp and paper industry, the textile industry, the chemical and electro-chemical industry, and mining.

Most industrial and manufacturing concerns are small, employing between 20 and 100 workers. A small number of industrial firms (about 600) have more than 100 employees, and only about 100 firms have a staff of more than 500 workers.

As industry has developed, the increasing problems of occupational hygiene and medical care called for the establishment of an industrial health service, with the following aims : (1) regular health control through periodical medical examinations, to protect and promote the health of the workers and other employees of industrial and other concerns ; (2) to promote industrial hygiene.

The former professor of hygiene at the University of Oslo, Carl Schioetz, was the pioneer in this work. In 1917 he tried to apply the principles mentioned above as a works doctor. Inspired by him and encouraged by his results, a few physicians interested in hygiene and occupational hygiene accepted in 1939 similar positions in other concerns. However, the work was still done on an experimental basis without a regular plan, and could therefore be of only limited value. During the years of World War II an increasing number of firms wished to employ works doctors, and so some of the physicians interested in hygiene got together to discuss what could be done.

They formulated the objectives of the industrial health service, both with regard to health control and to hygiene. The various aspects of the practical work were framed, including the design of a health card and regulations concerning the employment and salary of the physicians, with the purpose of creating a national uniform standard. The Norwegian industrial health service is based mainly upon the work of this group. The proposals which had been worked out during the years 1943 to 1945 were tested by a few practising physicians with good results. By the end of the war the plan of an industrial health service was wholeheartedly approved by the Norwegian Medical Association.

In addition to the approval of the physicians and their organizations, the plan needed the sanction and cooperation of the employers and employees.

Negotiations with the chief organizations of the employers and workers were started, when the general plan of the original committee was introduced and subsequently accepted with a few minor modifications. Furthermore, the two organizations expressed their desire to establish a council together with the Norwegian Medical Association. Thus the Board of the Industrial Health Service was established in the spring of 1946.

Organization

The Norwegian Industrial Health Service is not based upon legislation but on a voluntary mutual agreement between the three parties concerned, viz., the Norwegian Medical Association, the Norwegian Employers' Association, and the Norwegian Federation of Labour. The activities of this service are coordinated and administered by the Board of the Industrial Health Service, a tripartite administrative

* Based on a lecture given at WHO's first European seminar on occupational health at Leyden in 1952.

council. The activities of this council include the propagation of information about the industrial health service and the keeping of records of all the cooperating industrial concerns. It also directs the application of the plans according to the principles agreed upon, and gives counsel and advice on questions concerning the industrial health service.

The board has a permanent office, jointly financed by the three participating organizations. Individual firms may choose whether or not they wish to have a medical service in their plant. If participation is desired, the firm is required to comply with the policies of the board.

The General Plan

The general plan of the industrial health service calls for the establishment of a medical office with the necessary equipment and a waiting room at the plant, and the employment of doctors and nurses to carry out the work according to the adopted policies.

Expenses

All expenses connected with the plant health service, such as equipment, the surgery, remuneration of the physician and nurse, maintenance, etc., are met by the plant.

The cooperating industrial firms are also required to provide facilities for laboratory analysis at the plant. Great importance is attached to such an arrangement, not only to keep the industrial health service separated from general medical practice, but also because we want the physicians to be established at the plant. Only then can contact be maintained between the physicians, the management, and the workers, and only then can the physician devote himself fully to his work.

Working Hours of the Works Doctor

The working hours are stipulated by the Board of the Industrial Health Service according to the nature of the industry and the number of manual and clerical workers employed. In commercial firms and other firms without special problems of occupational hygiene, working hours have been fixed at one hour per week per 100 workers or less, and in industrial firms with special problems of occupational hygiene to two hours per week per 100 workers or less.

Salaries

The industrial medical officer is paid for his in-plant service per hour according to an adopted wage scale. Both working hours and other conditions must be approved by the Board of the Industrial Health Service in accordance with a standard contract.

Employment of Works Doctors

The following rules apply to the employment of works doctors in Norway: (1) Posts are advertised in accordance with conditions approved by the Board of the Industrial Health Service, and the Director General of Public Health nominates the three applicants considered best qualified, or (2) enquiries are made to the Board of the Industrial Health Service concerning its recommendation of candidates considered for employment by the firm before a definite choice is made.

All positions advertised shall be occupied only upon nomination. During the last five years 88% of the industrial firms introducing an industrial health service have employed works physicians according to the first plan whereas only 12% have used the second alternative.

The works physician is subordinated to the manager or other administrative head. The current employment policies are designed to offer the works physician adequate independence in his work. Most physicians are employed on a competitive basis and their duties and rights are clearly defined in printed instructions. These are known by the management and the staff alike. Norwegian works physicians therefore do not have the impression of " being bought and paid " by the employers. They have a free and independent position which allows them to retain an objective attitude towards both employers and workers.

Duties of the Works Physician

The works physician shall supervise the health of the employees by means of preventive medical examinations, health information, and other preventive measures. He shall examine all who are accepted for employment at the plant, and shall give a report to the management about their fitness for the work. Further, he shall regularly—preferably once a year—examine all employees at the plant.

Young workers, persons engaged in work dangerous to health, employees with partial disability resulting from disease or other causes, and persons frequently absent because of illness, receive special attention.

Standardized health cards and other forms are used for medical examinations.

It was realized that it would be of primary importance to make the medical examinations as

extensive and efficient as possible. This is assured as far as possible by using objective methods of examination and standardized health cards and other forms. It is emphasized that health control should not primarily include the negative aspects of the industrial health service, i.e., the detection of disease. The positive aspects, i.e., health information and prophylactic health care, are just as important. Great importance is attached to anamnestic data in connexion with the medical examinations, such as previous illness, family history, environmental situation, travel facilities, habits, hobbies, problems of personal and social adjustment.

By pre-employment examinations the works physician shall assist in determining the kind of work which is most suitable for each applicant on the basis of his physical and mental qualifications. In other words, he shall point out the abilities of the applicant rather than his disabilities. Many partly disabled have thus been helped to find suitable employment in industry.

Our original plan was to have all workers medically examined preferably once a year. We are now inclined to relax our previous standard for those between the ages of 20 and 40 years who do not present any sign of disease or special health problem at the initial examination. A medical examination every other or maybe every third year is now considered sufficient for this group. On the other hand all young workers and those partly disabled or with a weak constitution, as well as workers exposed to industrial health hazards, should be examined annually or at more frequent intervals. However, any employee has the opportunity of consulting the works physician at any time. All examinations shall take place during working hours without loss of wages.

Because it is not possible to carry out an effective programme of health control without a knowledge of the state of health of each worker during intervals between examinations, a special system of sickness absence reports has been introduced. In each case of sickness absence of more than three days' duration a confidential report about the disease, the length of absence, and the physician consulted shall be submitted to the works physician by the worker upon his return to work. This information is then recorded on the worker's health card so that the physician at all times may be kept informed about the state of health of the individual worker. In addition, these reports give a reliable picture of the nature and extent of diseases among the workers and in the plant as a whole. It is evident that this registration of sickness absences also yields valuable information in the field of occupational hygiene.

The works physician shall also be the works hygienist. He shall supervise the hygienic conditions in the plant by means of inspections. Furthermore, he shall investigate complaints about hygienic deficiencies, seek to prevent occupational diseases and accidents, as well as other industrial hazards, and work actively to promote hygiene and better working conditions in the plant.

Many works physicians have stimulated the management to establish a so-called health and safety board. The composition of these boards varies. Members are usually the works physician, one representative from the management, one from the manual workers, one from the other employees, one from the foremen, together with the safety engineer and the personnel manager. Through the activities of this health and safety board the hygienic conditions may be inspected and thoroughly studied. Complaints may be objectively investigated and recommendations for hygienic improvements presented to the management.

The works physician shall be the works consultant on medical hygiene. He shall serve as a consultant to the management, the foremen, and the production committee, and give advice in matters of sick-leave, transfer to other work, adaptation of the work on medical grounds, and other questions of a medico-hygienic nature.

This part of the work has been a great help to management, which is increasingly appreciative of medical advice on questions of employment, personnel administration, sick-leave, pensions etc.

In cooperation with the industrial management and the supervisors, the works physician shall seek to combat absences due to malingering among the employees. He has the right to examine anyone suspected of malingering, and should by educational and informative means discourage abuse and, if needed, give warnings. The management, the supervisors, and the physician consulted shall be notified in cases of serious abuse of sickness absence or leave.

To facilitate the control of sickness absence, a system of individual registration of absence due to sickness or other causes has been introduced. Each absence is recorded in one of three groups : sickness absence, granted leave, or "shirking". The individual records thus give a revealing picture of the health and working capacity of each employee, enabling the works physician to carry out an efficient control of the workers in the specified points. The records give an annual cumulative survey of the total absence in the plant and of the distribution of absence in the various departments and groups of workers. Frequencies of absence may

thus be compared within the plant and with comparable figures from other plants.

Like other physicians, the works physician is under the oath of secrecy. Information about the nature of disease in any employee must not be given to the management or to fellow workers without the consent of the individual concerned. The health cards and other information about the employees shall be locked up and be accessible only to the works physician and his staff who are also under the oath of secrecy.

The works physicians shall carry out their work in cooperation with private practitioners. Persons needing medical attention who have their own private doctor should be referred to him. The patient may also be referred directly to a specialist when required. In such cases the physician regularly consulted by the patient should always be informed about the results of the special examination.

It is a general agreement that the works physician shall not give regular medical treatment in his works surgery. But he may and should treat injuries and other conditions requiring immediate attention ; he may also give attention to occupational diseases not involving loss of work, and minor ailments, which may be treated instantly. No payment from the patient, the plant, or medical insurance is to be received for treatment in such instances.

There are two reasons for the adoption of this policy : the first is in the interest of the private practitioners ; the second concerns the scope of the industrial health service. We have been very anxious to ensure that physicians shall devote their time to preventive medical examinations and health guidance, as well as to hygienic work in the plant.

Another duty of the works physician is the preparation of an annual report to the industrial management. One copy is submitted to the Board of the Industrial Health Service and contributes to a broad evaluation of the efficiency of the industrial health service.

The purpose of this report is primarily to stimulate the works physicians to acquaint themselves with the problems of their respective industries and to study the effects of their work. The second purpose is to collect information in the field of industrial hygiene.

The Norwegian Industrial Medical Association has prepared a standard for annual industrial health service reports to facilitate statistical studies. The current standard report has three parts.

The first part is a general survey of the hygienic conditions in the plant as a whole, with information about the nature of the work and the personnel, and a report of the general medical examinations.

The second part includes the results of the individual tests which form part of the medical examination, such as tuberculin tests, B.C.G. vaccination, haemoglobin and blood pressure determinations, measurements of weight, serological tests.

The third part is devoted to statistics of absence. The report shows the absence among manual and clerical workers, men and women, and the various age groups respectively. A report of absence due to various diseases according to a specified grouping is also included in this part, together with a report of occupational diseases and accidents, granted leaves, and " shirking ". These reports are forwarded to the Board of Industrial Health, where they are included in national statistics.

Experience of the Service

As this industrial health service has existed for nearly a decade it seems to be worth while to summarize some of the experience gained during this period.

The policies which have been followed up to the present seem to be well suited to national conditions. Health authorities, the physicians, the employers, and the employees have supported the plan with very few exceptions. Indeed, no other social or hygienic scheme can demonstrate a similar rapid expansion and development.

DEVELOPMENT OF THE INDUSTRIAL HEALTH SERVICE IN NORWAY 1944–1951

Date	Participating Plants	Workers Included
Before 1944	32	Approx. 12,800
1944	46	14,315
1945	63	20,321
1946	100	39,678
1947	263	74,554
1948	375	99,616
1949	435	125,339
1950	498	141,502
1951	542	167,687
1952	572	176,164
1953	653	186,490

Our industrial health service has also stimulated and formed a pattern for the expansion of public health care to other population groups, such as housewives and students.

There are many reasons for this rapid development. It is evident that the social consciousness and spirit of cooperation prevalent during World War II and the initial post-war period and the subsequent rise in industry and trade have played an important part. The fact that our industrial health service is voluntary and based on a mutual tripartite agreement, and that it accords with modern concepts of

hygiene and social medicine, has laid the foundation for general recognition and support, and has hastened the expansion of the programme. It seems that a better solution to the financial and professional administrative problems could not have been found, and that we were most fortunate in arriving at this solution at the very start.

Not only private firms but also municipal and state concerns have participated in the plan. Industrial health services have also been adopted by a number of business concerns, banks, etc., and not only by manufacturing plants.

That the employers are on the whole satisfied with the plan is evident from their support. Most employers regard the industrial health service as a valuable asset and consider the expenses involved to be a good investment.

The attitude of the workers and personnel is best demonstrated by the fact that there is almost 100% attendance at the medical examinations, which are entirely voluntary, and that the workers themselves to a large extent apply to the management for the introduction of the industrial health service in their plant.

Our physicians have shown great interest in the industrial health service. Approximately 600 physicians have completed a training course for works physicians, and the Norwegian Industrial Medical Association now has a membership of 260 active works physicians. The works health service supplements and fits well into the pattern of our medical organization, and good cooperation exists between the works physician and the private practitioners. Most works physicians work on a part-time basis from one to 24 hours per week. Only three are doing full-time in-plant service.

The industrial physicians have generally been well qualified for their work, both with regard to preventive medical examinations and health guidance. It might be assumed that the so-called family doctors would be those best qualified for preventive health work, because of their knowledge of the previous state of health of the employees and their home environment. Our experiences show that the majority of the employees attend the medical examinations at the works health department. The same amount of cooperation would hardly result if these examinations were to be carried out by the family doctor.

By our present system the works physician quickly adjusts himself to the demands of prophylactic medical work, and will get acquainted with the workers, the plant, and the work through his in-plant service. This knowledge of the occupational milieu and problems is as important as the knowledge of the home environment. Also, the first interview and the subsequent consultations, as well as the sickness absence reports, will soon enable the works physician to form a true picture of the previous and present state of health of the workers and their families.

Values and Costs

The question of the value of industrial health control cannot be definitely answered because so many factors are imponderable. We shall for a long time have to rely on personal impressions more than on statistical data. However, it seems quite clear to those with some years of experience in industrial health work that industrial health care is an important factor in the efforts towards improved physical and mental health in the general public.

A few results of the health work in Norwegian industry may serve to throw some light on the question. The discovery of disease is only a part of industrial health care, but still an important one. The question most often asked is how efficient is an industrial health service for diagnostic and therapeutic purposes. Many works physicians have followed our request to report the various diseases, defects, and anomalies discovered by routine examinations at the plant and in how many instances treatment had not been given previously. The results for the years 1948 and 1949 are shown in Table 1.

The various groups of diseases as a cause of absence among men and women, and manual and clerical workers in 1949 are shown in Table 2. The figures represent the percentage distribution of absence of more than three days' duration according to various diseases.

Exact figures of costs cannot be given, because the expenses vary according to the size, needs, and financial resources of the various industries. It is calculated that the average cost per head per year amounts to 20 to 30 Norwegian kroner (20–30s.).

A primary aim is to discover hitherto unknown cases of diseases among the workers examined. A second objective is to assist the workers needing medical attention in securing early and correct treatment, and to spread information about medical advances, and thus establish a popular confidence in the modern methods and facilities available. We frequently observe in our practice that the popular conception of medical therapeutic facilities is outmoded sometimes by 20 to 30 years. It is our privilege and our duty to inform the population about these possibilities. The third aim is to study the incidence and distribution of various diseases and anomalies among the workers. Our industrial

TABLE 1

DISEASES, DEFECTS, AND ANOMALIES DETECTED ON ROUTINE INDUSTRIAL MEDICAL EXAMINATION

Disease	62,311 Examinations in 1948 and 1949	
	Number of Cases	Not Previously Treated
Tuberculous diseases	817	160
Venereal diseases	333	135
Other infectious diseases	215	78
Malignant tumours	65	41
Diseases of the respiratory organs	3,392	1,310
Diseases of the heart and circulatory system	4,117	1,720
Diseases of the digestive system	3,083	722
Diseases of the nervous system, mental diseases	1,241	277
Diseases of the urinary and sexual organs (not V.D.)	1,225	590
Diseases associated with pregnancy	31	22
Skin diseases	2,671	981
Rheumatic diseases, diseases of the skeletal system	7,271	2,465
Diseases of the eye	3,749	1,001
Diseases of the ear	1,644	417
Asthenia	413	108
Metabolic and nutritive diseases	718	192
Diseases of the blood	1,359	914
Injuries and sequelae of injuries	1,087	267
Other diseases	1,130	239

Hypertension, defined as a systolic pressure above 160 mm., was found in 1·4% of male workers under 40 years of age, in 12% between the ages of 40 and 59 years, and in 18% above 60 years. The corresponding figures for women were 0·7, 17, and 42% respectively.

A diastolic pressure above 100 mm. was found in 2·5, 12, and 27% of male workers in the corresponding groups, and among women in 0·5, 13, and 33% respectively.

Anaemia, defined as a haemoglobin content below 90% for men and below 80% for women, was found in 3·4% of the men and 4% of women workers. Pathologically increased sedimentation rates, above 20 mm. for men and 40 mm. for women, were found in 4% of the men and 11% of women workers.

A positive *Meinicke reaction* was found in 1·8% of all workers in 1948 and 0·8% in 1949.

health service has been organized to provide for all these aspects of health care.

Tables 1 and 2 illustrate the incidence of diseases detected on routine industrial examination. Considering the fact that those examined are presumably healthy individuals, these figures clearly indicate the value of these examinations. This is further confirmed by the fact that between 10 and 15% of the workers examined are found to be in need of medical treatment for some ailment.

However, attempts to evaluate these services in their economic relationship are futile. The values represented cannot be counted in money. What does it mean to the individual concerned, to the plant, and to society that the unknown presence of a disease is revealed so that the disease may be treated in time? According to what economic scale should attempts be made to evaluate, for example, the detection of 350 cases of tuberculosis, 250 cases of syphilis, and 110 cases of cancer, per year among the 165,000 workers included in the industrial health service?

In addition to these diseases many other major and minor ailments are found.

The detection of disease, however, is only one aspect of industrial health care, or what might be called the negative aspect. The positive aspect is the health information programme and prophylactic measures. The value of the health guidance programme lies in the possibilities of making the modern therapeutic methods known to the public and the establishment of an intimate contact between the physician and the workers. In times when mental and nervous disturbances seem to become more and more prevalent, it is of essential value for the workers to have a physician to whom they can confide their troubles and fears. This cannot be evaluated in terms of financial gain. The same applies to the prophylactic measures such as vaccinations, relaxation exercises, physical exercise and massage, as well as the personal influence of the physician with regard to the preservation of good health.

The regular medical examination in the various firms will also be of great value by showing the incidence and influence of various diseases among the adult population.

The work of the physician to promote better hygienic conditions in the plant also merits attention. The function of the physician as the active hygienist of the plant was not as much stressed

TABLE 2

DISEASES CAUSING ABSENCE IN MANUAL AND CLERICAL WORKERS

Disease	Men		Women	
	Manual Workers	Clerical Workers	Manual Workers	Clerical Workers
Tuberculous diseases	7·5	9·2	3·4	4·8
Venereal diseases	0·4	0·07	0·1	0
Other infectious diseases	2·3	1·2	2·7	0·9
Malignant tumours	1·0	1·3	0·9	1·3
Diseases of the respiratory organs	18·7	24·6	17·4	18·7
Diseases of the heart and circulatory system	4·8	6·7	3·5	3·6
Diseases of the digestive system	10·4	9·7	7·1	5·9
Diseases of the nervous system, mental diseases	5·5	9·0	8·0	10·5
Diseases of the urinary and sexual organs (not V.D.)	2·4	3·3	6·4	7·2
Diseases associated with pregnancy	—	—	2·8	1·5
Skin diseases	2·2	1·2	3·2	1·5
Rheumatic diseases, diseases of the skeletal system	18·5	17·0	23·0	31·4
Diseases of the eye	1·2	1·1	0·8	0·4
Diseases of the ear	0·7	1·2	0·9	0·6
Asthenia	0·3	0·1	2·3	1·0
Metabolic and nutritive diseases	0·4	0·2	0·2	0·6
Diseases of the blood	0·2	0·1	2·6	1·0
Injuries and sequelae of injuries	17·7	12·1	8·2	6·6
Other diseases	5·8	2·0	6·4	2·5

previously as it is today. Accordingly, the work of the earlier physicians was almost entirely confined to health control. This, however, was a necessary and natural step in the development. During the initial years of their work, the works physicians had to concentrate on their medical duties alone and become acquainted with the workers and the various manufacturing processes at the plant.

A marked change has taken place during recent years, as the physicians are now more actively engaged in promoting hygienic conditions.

It might be argued whether a works physician receiving payment from the firm can give efficient service in the field of occupational hygiene. On rare occasions the management have actually created difficulties. Those employers who decide to appoint an industrial health physician are fully informed about the various aspects of the industrial health service as agreed upon, including occupational hygiene. Initiative in this field on the part of the works physician is expected and any proposals from him in this connexion will usually receive positive consideration. Experiences seem to indicate that there does not exist any serious obstacle of this nature.

It might also be discussed whether or not works physicians, most of whom are private practitioners, specialists, and public medical officers without special training in occupational hygiene, possess the necessary qualifications for preventing occupational diseases and promoting occupational hygiene. Special courses for physicians and medical students have been given, but these do not give adequate and complete preparation in the field. The reason why we cannot yet offer complete training in occupational hygiene is that we do not have an institute of occupational hygiene which fulfils our present needs.

In spite of these defects, a number of works physicians have performed very admirable hygienic sanitation work in their respective plants. Many investigations have been initiated to solve special problems and a number of various scientific research projects have been completed and published. At the larger industrial concerns with laboratories the physician may carry out such investigations at the plant with the assistance of the engineers. Most works physicians, however, must rely on assistance from the National Labour inspectorate and our Institute of Occupational Health and the out-patient department of occupational diseases in Oslo.

In addition to investigations, such as determinations of the contents of poisonous substances in the blood, urine, and air, and dust analyses, the work includes regular inspections of lavatories, lunchrooms, wardrobes, baths and showers, lighting, chairs, temperature in the plant, and, most important, order and cleanliness. Complaints from the workers with respect to hygienic deficiencies are immediately investigated. This is an important part of the duties of the works physician. The work of physicians, nurses, and welfare workers in nearly 600 firms adds up to a considerable contribution to industrial health care.

Industrial and Public Health Services

The major part of preventive health care in Norway is carried out by the local boards of health and by the public medical officers under the administrative authority of the Directorate of Health. These various organs of the public health services are connected with industrial health care in various ways.

Full cooperation has existed with the Director General of Public Health, who is usually the nominating party in the employment of works physicians.

Many of the public medical officers take part in hygienic work as part-time works physicians. The Directorate of Health works towards the objective of creating a full-time office for public health work so that those engaged can fully devote their time to this type of work, by combining public and industrial health duties. Within a four-months course for public health officers three weeks' instruction in industrial medicine and hygiene is given.

Cooperation has also been established between the works physicians and the local boards of health, especially in the field of tuberculosis control. In certain locations where health centres have been established the industrial medical examinations may be carried out at the centre.

At first it seems to be a logical idea that the industrial health service should belong to the work and administrative authority of the boards of health. As the industrial health service is completely supported by the industrial firms themselves, this transfer is not practicable. It would, however, be desirable to establish a closer contact between the boards of health and the industrial health service. This might be accomplished by making the reports, submitted by the works physicians to the Board of Industrial Health Service, available also to the local board of health. The board of health might also take the initiative in promoting this contact by coordinating their investigations with those included in the industrial health work by furnishing material for health information suggesting the form of the health cards, and by contributing toward technical equipment and service.

That the industrial health service is administered

by the independent Board of the Industrial Health Service is both a weakness and a strength. The weakness consists in the absence of laws and the resulting dependence on mutual tripartite agreement. Another weak point is the lack of coordination with other public health work, which accounts for some overlapping or duplication of certain projects. The strength lies in the voluntary basis and the flexibility of policies which facilitates changes as necessitated by medical and social developments.

The State Labour and Factory Inspection Board and the Industrial Health Service

In accordance with our law on labour and factory inspection, a local industrial supervisory committee shall be established in each municipality to supervise the hygienic conditions in industrial and other concerns within the district. The central authority is vested in the State Labour and Factory Inspection Board, which from the very start of the industrial health service has cooperated with the works physicians. This is partly due to the fact that physicians from the State Labour and Factory Inspection Board have taken part in formulating the policies for the industrial health service. There has never existed any noticeable friction between the works physicians and this board, or any overlapping in their work worth mentioning. The works physicians help the board in much the same way as the board gives practical and scientific assistance to the works physicians. The survey of occupational diseases throughout the entire country resulting from the work of the works physicians is only one example of the kind of assistance which these can give to the inspectorate.

If our labour and factory inspection had been expanded with the services of the additional number of physicians, chemists, engineers, and inspectors who could effectively serve all firms throughout our country, it might possibly have taken over all the investigations of occupational hygiene necessary in industry. However, it could not have replaced the individual hygienic work of the works physicians. The State Labour and Factory Inspection Board has therefore encouraged the firms to introduce the industrial health service as a means of improving working conditions. Our main concern is not, therefore, that of favouring one at the expense of the other, but of continued cooperation in the belief that further development of both the industrial health service and the industrial supervisory organization is that best serving the needs of occupational hygiene and public health.

Still closer cooperation might, however, be desirable, for example, by sharing reports about hygienic conditions and sickness absences with the Labour and Factory Inspection Board, and by a joint inspection in firms with a works physician.

Conclusion

This form of industrial health service has sprung out of the special conditions in Norway, and has enabled us to establish an industrial health service without danger of weakening the medical services as a whole. Needless to say, any lack of physicians would have prevented the creation of this service, and our system is therefore not advisable in a country with a shortage of physicians.

Another distinguishing feature in this system is that the geographical extension of our country and the difficult communications in many places have necessitated the delegation of the preventive health work to the private physicians and only to a smaller extent to health centres and institutes.

A third feature is that our industrial supervision is not so far developed and efficient as in some other countries, and cannot offer the same service as similar organizations in more densely populated countries, even if it had been further developed.

Our experiences so far indicate that the system we have chosen will survive. This does not mean that our industrial health service will continue in its present form. On the contrary, we shall endeavour to improve it as desirable and necessary on the basis of changes in the medical and social views and according to experience.

However, the two basic principles upon which the industrial health service is founded, namely, health control of the employees and hygienic work in the plant, have been sound and efficient.

That we have recognized the same principles in the industrial health services of other countries seems to confirm their value.

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FATAL EMPHYSEMA IN TWO MEN MAKING A COPPER CADMIUM ALLOY

BY

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This paper gives an account of two patients who died of emphysema after working for a few years in a small foundry making various copper alloys, including one of copper cadmium.

Acute cadmium poisoning has been recognized for many years, and the injurious effects of the metal fume upon the respiratory tract after single sharp exposures have been reported on several occasions. The earlier literature was well summarized by Prodan (1932). A report of 15 cases including two deaths was made by Bulmer and his fellow workers in 1938.* The clinical picture was one of intense respiratory irritation, causing praecordial pain and severe dyspnoea. This came on a few hours after exposure which at the time did not cause sufficient discomfort to make the men leave their work. In the fatal cases death occurred in five to eight days; no signs of systemic poisoning were noted. Wahle (1932) recorded acute poisoning in a man making copper cadmium alloy; he had praecordial and epigastric pain, with vomiting and severe dyspnoea. The possibility of chronic cadmium poisoning occurring in men exposed to repeated small doses of cadmium metal fume was first suggested by Hardy and Skinner (1947). They recorded undue fatigue and vague gastro-intestinal symptoms in five men subjected to minor degrees of cadmium exposure. Friberg (1950) first drew attention to an unusual proteinuria in workers exposed to cadmium oxide and at the same time described anosmia and emphysema in the same group. Emphysema was confirmed at the necropsy of one patient and reduced respiratory efficiency was found in others. Baader (1951) made similar observations in a group of men exposed to cadmium oxide.

Process

Our two patients were members of a group of some 20 men making copper alloys. The process suspected of being responsible for their condition consisted of melting copper (melting point 1083° C) and adding small quantities of cadmium (melting point 321° C, boiling point 767° C). The men were provided with respirators and the process was carried out under exhaust ventilation. But at the critical time of adding the cadmium, which immediately boiled, the mixture was stirred and the men were exposed to considerable quantities of fume. They stood on a platform above the molten mixture and pushed aside the exhaust hood to make it easier to stir. Determinations of cadmium in the general atmosphere of the foundry carried out over the period 1951–53 by the works chemist were 0·11, 0·09, 0·16, 0·07, 0·21, 0·4, 0·17, 0·14 mg./cm.

Case Histories

Case 1.—A man aged 53 complained of severe dyspnoea. On leaving school he became a boot repairer until he reached the age of 29 in 1927, when he joined the foundry where he worked for the rest of his life. His earlier years were spent as a mould attendant on various alloys, mostly brass, and he started as a furnace man making the copper cadmium alloy in 1940; from this time until he gave up work he was occupied extensively on this process.

He was well until some 18 months after starting on the copper cadmium mix when he noticed that he was becoming breathless and was unduly exhausted at the end of the day, complaining of fatigue and a poor appetite. He continued at work but about six months later (in 1942) he attended his doctor who sent him to the chest clinic where, however, *x*-ray and sputum examination showed no abnormality. A few weeks later he returned to work but failed to improve and by the end of 1942 found that he could not get to work because of breathlessness. After 11 months away from work he attempted to go back but soon broke down again and gave up all work in 1944. After this he was more or less confined to bed. His doctor reports that he did not appear to change very much over the next few years. He had not previously suffered from a chronic cough nor from asthma.

He was examined at home in 1951, and cooperated

* The working conditions responsible were reconstructed and studied in detail by Barrett and Card in 1947.

well, but refused admission to hospital. He could lie flat without discomfort but movement in bed produced breathlessness. He was slightly cyanosed ; there was no clubbing, kyphosis, or chest deformity and his chest expansion was ½ in. Physical signs of advanced emphysema were present but there were no adventitious sounds. There was no evidence of cardiac disease ; his blood pressure was 110/70 mm. Hg. No abnormality was detected in the urine but the test for protein as described by Friberg (*op. cit.*) was not carried out. The patient's doctor reported that the patient died a year later from cor pulmonale. No post-mortem examination was made.

Case 2.—A man aged 50 complained of severe dyspnoea. He started work as a boy in a coal-mine, eventually became a collier and worked at the coal face for 16 years until 1930. In the period 1930–39 his employment was uncertain ; he worked sometimes in the pit and sometimes as a builder's labourer. He served in the army from 1939 to 1945 and was discharged fit. In September, 1945, he joined the foundry where he worked as an assistant moulder for nine months until May, 1946, when he left to return to the coal-mine. Here he worked for a year after which he returned to the foundry and worked as a furnace man for 14 months until October, 1948, when he gave up on account of breathlessness on exertion. He did light work away from the foundry for six months until April, 1949, when dyspnoea again forced him to stop work. Seven weeks later he returned to a sedentary job for a few months. In January, 1950, he gave up work altogether.

The patient was first seen in hospital in October, 1950, when he gave the following history. He had always been well until the summer of 1948 when he complained of fatigue, loss of appetite, and shortness of breath. His dyspnoea increased and forced him to give up work. On admission to hospital he was wasted (height 5 ft. 5 in., weight 100 lb.) and slightly cyanosed. His sense of smell was unaffected ; there was no clubbing, cough or sputum, but there was some thoracic kyphosis. Chest expansion was 2½ in. and there were physical signs of advanced emphysema with a few high-pitched rhonchi. A radiograph showed emphysema only. His vital capacity was 2,100 ml. No abnormality was detected in the cardiovascular system and the blood pressure was 140/90 mm. Hg. An electrocardiogram showed that the axis was towards the right limit of normal. The P waves in lead II and in the foot lead were of high voltage and the R waves in the left praecordial leads were of low voltage. This finding is consistent with, but not necessarily diagnostic of, cor pulmonale. The urine showed no proteinuria or other abnormality.

Laboratory Examination.—A blood count gave Hb 15·1 g./100 ml., R.B.C.s 5·2 million, and W.B.C.s 10,300 (60% polymorphs). The erythrocyte sedimentation rate was 11 mm. in one hour (Wintrobe), serum albumin level 4·4%, serum globulin level 2·0%, and blood urea level 28 mg.%. Clearance was 100% normal. The galactose index was 184.

The patient was discharged from hospital in November, 1950. His dyspnoea increased slowly over the next two years, confining him to bed, and he died in January, 1953.

Necropsy Findings.—The necropsy was performed 30 hours after death. The findings of note were as follows :

The pleural sacs contained no fluid ; there were old fibrous adhesions on the lateral and posterior aspects of the lower lobe of the right lung. Both lungs were voluminous, their anterior borders meeting over the pericardial sac. The right lung weighed 370 g. ; the left appeared of similar weight, but was injected with formol-saline without being weighed. The anterior borders were rounded, but no bullae were visible. The visceral pleura was pigmented with carbon more than the average. The left lung, after injection of the bronchial tree with formol-saline, showed on section (Figs. 1 to 3) extremely severe emphysema. This was widespread throughout the lung ; in many places the lung tissue was reduced to a very coarse spongework, the individual cavities measuring up to 1·5 cm. in diameter. An unusual feature, however, was that the emphysema tended to spare a narrow zone, 0·5 to 2 cm. wide, just under the pleura so that bullae did not present on the surface. Carbon pigmentation was of more than average degree, but not sufficient to suggest a primary anthraco-emphysema. There was no sign of pneumonia, tuberculosis, or fibrosis. There was a small, recent haemorrhagic infarct in the lower lobe. The bronchi contained a little cloudy mucus but there was no congestion of the mucosa.

Whole sections of the left lung were prepared by the method of Gough, James, and Wentworth (1949) and in these the lung was severely destroyed (Fig. 4). The right lung showed a similar picture. The hilar and tracheo-bronchial lymph nodes were normal apart from anthracosis. The main pulmonary arteries showed slight atheromatous flecking. The pericardium appeared healthy and the coronary arteries showed only slight atheroma. The heart was slightly enlarged. The right ventricle was moderately hypertrophied and slightly dilated ; the other chambers appeared normal. The myocardium showed no focal lesions, and the valve cusps were healthy. The heart weighed 320 g. (left ventricle 74 g., right ventricle 80 g., septum 64 g.) ; the wall of the left ventricle was 11 mm. and that of the right ventricle 6 mm. thick.

The prostate was slightly swollen, and of a patchy, yellowish colour on section. Apart from moderate congestion in the liver, spleen, and kidneys, the abdominal viscera appeared normal. The stomach and intestine were not dilated.

The brain and spinal cord and the bone marrow appeared normal.

Histology.—Sections from various areas (upper, lower, central, and peripheral) of both lungs confirmed widespread, extremely advanced emphysema. In some fields, bronchioles, arterioles, venules, and interlobular septa were the only remaining tissue. Some of the bronchi and bronchioles showed inflammatory changes with lymphocytes and plasma cells infiltrating their walls, and with mucin and a few polymorphs in the lumina ;

FIG. 1.—Left lung (after formol-saline injection) showing the absence of surface bullae.

FIG. 2.—The cut surface of the same lung, showing the very severe emphysema with sparing of the peripheral zone.

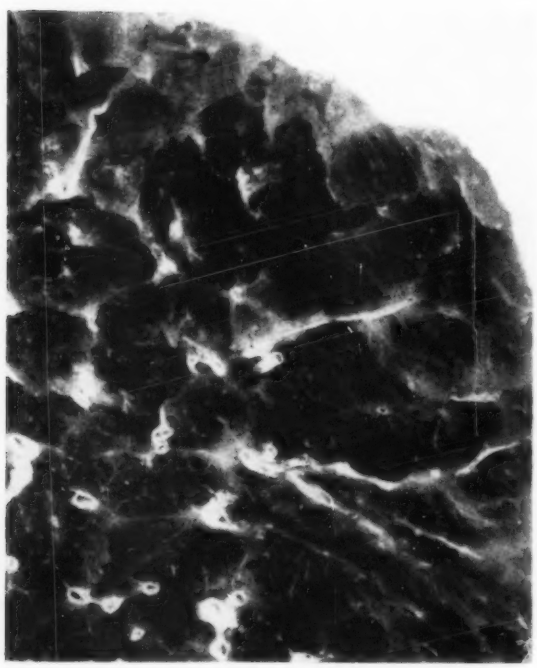

FIG. 3.—An enlargement from a part of Fig. 2.

FIG. 4.—Whole section of the left lung showing severe destruction of lung tissue.

but chronic bronchitis was neither universal nor severe. There was no peribronchial fibrosis or fibrosis of the lung tissue, nor was there any interstitial or alveolar pneumonia. The elastic tissue of the surviving alveolar septa appeared normal and no significant change could be seen in the blood vessels.

A mild chronic inflammatory reaction of the mucosa was seen in a section from the lower end of the trachea.

The right ventricular myocardium showed hypertrophy of muscle fibres and a mild, fairly uniformly distributed fatty degeneration. There were also a few small foci of early necrosis in the inner part of the myocardium. There was no fibrosis. The left ventricular myocardium showed only considerable lipochrome deposition.

The liver was congested, with a considerable lipochrome deposition and a mild degree of fairly uniformly distributed fatty degeneration. There was no centrilobular atrophy of liver cells but in many lobules early centrilobular necrosis could be detected.

There was a diffuse, acute, suppurative prostatitis.

A well marked chronic gastritis was present. The corpus mucosa showed considerable glandular atrophy, metaplasia of glands to intestinal type, and marked round-cell infiltration. No significant abnormalities were seen in sections of the spleen, pancreas, adrenal, thyroid, hypophysis, brain (frontal and hippocampal cortex, basal ganglia, and mid-brain), spinal cord, bladder, seminal vesicles, oesophagus, small and large intestine, and sternal bone marrow.

Histochemical Investigations.—Hörstebrock's dithizone method (1953) failed to demonstrate cadmium in sections of lung, liver, and spleen.

Chemical Analyses.—Determinations of the cadmium content of various organs were carried out using a dithizone procedure (Setterlind and Krause, 1943) after wet oxidation (Fairhall and Prodan, 1931).

CADMIUM CONTENT OF VARIOUS ORGANS

Organ	Cadmium Concentration (mg. 100 g. fresh tissue)
Lung	277
Kidney	233
Pancreas	193
Small intestine	187
Spleen	143
Liver	25
Brain	0

No cadmium could be detected in bone (femur), possibly owing to the bulky deposit of calcium sulphate.

Values for normal tissues have not yet been established but these figures offer interesting comparison with those of Friberg (1950) who found 600 mg. per 100 g. in the lungs but comparatively much larger amounts in the liver (average 2,300) and kidneys (average 2,200). Thus only the concentration of cadmium in the lungs is in the same range as reported by that author.

The necropsy findings indicate that death was due to the anoxia produced by severe emphysema, with terminal right heart failure, possibly precipitated by bacterial toxaemia from acute prostatitis. The cause of the latter is obscure ; no bacteria were identified.

Discussion

Two deaths from emphysema in a group of some 20 men is not in itself a remarkable event. When, however, the emphysema has arisen with no previous history of asthma or bronchitis and gives rise to severe disability in a very short period, it cannot be regarded as a usual form of the disease.

The reputation of cadmium fume as a respiratory irritant is such as to suggest it was the responsible agent ; furthermore, the cadmium content of the lung supports this thesis. The absence of proteinuria, in the one case in which it was sought, is not remarkable because the patient's exposure to cadmium was shorter than four years. Friberg (*op. cit.*), who describes the condition, did not find it in workmen with so short an exposure.

The pathological picture in our second case cannot, of course, be regarded as pathognomonic of chronic poisoning by cadmium or other metallic fume. Little is known of the pathology of chronic cadmium poisoning in man. Friberg (1950) and Baader (1951) have each reported one fatal case with necropsy findings. In both instances emphysema was prominent but it was in each case associated with severe bronchitis which makes it difficult to assess the part played by cadmium in its aetiology.

Our second case resembles these two only in that severe emphysema and cor pulmonale were prominent features. In our patient the emphysema appears to have been of an unusual type being characterized by a peculiar sparing of the peripheral zone of the lung which neither Friberg nor Baader recorded ; and the inflammatory changes in the lung were also much less marked in our case. Both Friberg and Baader found much greater concentrations of cadmium in the organs, especially in the liver and kidney, than we did ; but the conditions of exposure of their cases were very different. Their patients had been working for many years under conditions of continuous exposure to cadmium oxide, roughly estimated in Friberg's case as having been of the order of 3 to 15 mg. per cm. In our case the general exposure to cadmium was a fraction of this (0·1–0·4 mg. per cm.) and it extended over a much shorter period ; there was, however, an additional and different type of exposure, namely to cadmium metal fume (i.e., the freshly formed oxide) which was breathed in high concentration for very short periods.

It is well known that the action of certain freshly formed metallic oxides on the respiratory tract may be different from that produced by the stable oxide.

The best-known example is provided by zinc fume which can produce an acute reaction in the lung associated with pyrexia and leucocytosis, while the stable oxide of zinc can be inhaled in much larger quantities with no such effect. This difference has been explained by the much smaller particle size of the fume and its absolute dryness (Drinker, 1922).

The acute effects of cadmium fume on the respiratory tract have been referred to above. Our patients were repeatedly exposed to small quantities of freshly formed cadmium oxide produced from boiling cadmium, and our findings point to a local lesion in the respiratory tract and not to systemic poisoning.

Summary

Two fatal cases of emphysema are reported in men engaged for less than two years in making a copper cadmium alloy. This involved very short periods of exposure to cadmium fume. Necropsy on one case disclosed a severe and unusual type of emphysema which spared the periphery of the lung. There was no evidence of systemic cadmium poisoning and it is postulated that the condition of the lung was the result of the local action of freshly formed cadmium oxide.

We are indebted to Professor J. Gough of Cardiff for the whole lung section ; to Dr. Hörstebrock, of the Institute of Pathology, University of Münster, for details of his histochemical method for the detection of cadmium and for additional data on the necropsy on Professor Baader's case ; to Dr. J. E. Kench for the biochemical determinations of cadmium in the tissues ; and to Dr. H. A. Picton for details of the patients' histories.

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A STUDY OF BOILS AT THREE COLLIERIES

BY

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From the National Coal Board (East Midlands Division)

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It has been suggested that environmental conditions in coal mining such as high temperature, humidity, and slow movement of air, are associated with furunculosis. Boyd (1949) observed that certain pits were characterized by repeated outbreaks of boils. Schwartz and Warren (1941) and Schwartz and Goldsmith (1944) give furunculosis pride of place among the skin lesions of coal miners.

Apart from the general relationship between an adverse mine climate and furunculosis, little detailed information can be gathered from the literature about the natural history of boils as they affect the miner. The following investigation was, therefore, undertaken to find out more about this disorder among coal miners.

Colliery Survey

Three pits, where boils seemed prevalent, were chosen for study. They may be described thus :

Pit	Depth in Feet	Average No. Employed	Method of Working
A	3300	1700	Partly mechanized
B	2100	1600	Highly mechanized
C	720–900	1300	Coal, machine-cut but hand-loaded

Several faces of these three pits showed considerable variation in mine climate during the period of this study ; the ventilation rate ranged between 140 and 370 feet per minute, and the wet bulb temperatures ranged between 70 degrees and 80 degrees.

All three collieries have a medical centre under the charge of a state registered nurse who keeps individual medical records. These records for the two-year period 1950–1951 were examined and the sections relating to boils were analysed, particular attention being paid to the boil rate in the different occupational groups, the site of the lesion, and the recurrence rate. Boils were only recorded when they were reported voluntarily by the mineworkers themselves. As all three medical centres were popular, it is unlikely that there was any substantial difference in reporting between the three pits. Further, it is most improbable that there were any systematic differences in reporting between the various occupational groups.

Boil Rate by Occupational Groups

The mineworkers were divided in the first instance into three broad occupational groups : coal-face workers, men employed elsewhere below ground, and surface workers. The boil rate among these three groups is shown in Table 1.

TABLE 1
BOIL RATE BY OCCUPATIONAL GROUPS

Pit	Coal Face Workers			Men Employed Elsewhere below Ground			Surface Workers			Total		
	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%
A	134	769	17·4	43	595	7·2	17	358	4·7	194	1722	11·3
B	97	521	18·6	61	713	8·5	35	349	10·0	193	1583	12·2
C	132	582	22·7	48	453	10·5	39	298	13·1	219	1333	16·5
Total	363	1872	19·4	152	1761	8·6	91	1005	9·0	606	4638	13·1

TABLE 2
BOIL RATE OF FACE WORKERS

Pit	Colliers			Rippers			Packers			Others			Total Boils at Each Coal Face
	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%	Men with Boils	Average No. Employed	%	
A	106	458	23·1	11	101	10·9	9	91	9·9	8	119	6·7	134
B	43	157	27·4	28	97	28·9	18	100	18·0	8	167	4·8	97
C	61	211	28·9	29	82	35·3	18	83	21·7	24	206	11·6	132
Total	210	826	25·4	68	280	24·3	45	274	16·4	40	492	8·1	363

As the figures relate only to the first occasion when a man reported a boil, the rate of 13·1% implies that one man in eight had a boil within the two-year period under review. The boil rate is lowest at Colliery A and highest at Colliery C for all categories of workers. There was no marked difference in the boil rate between men employed on the surface and underground away from the face, but the rate among face workers was significantly higher than that among the two former groups.

In Table 2 face workers are sub-divided into colliers, rippers, and others. Colliers actually load the coal on to the conveyor belt either by hand or mechanically. Rippers drive the main roadway as the face advances, and are responsible for its preservation. Packers fill in the waste after the coal has been removed. Others on the coalface comprise a miscellaneous group of shotfirers, conveyor erectors, borers, and cutters.

It will be seen that colliers and rippers were more commonly affected by boils than packers and "others". The rippers and the packers showed a wide range in their boil rates as between the three pits. "Other" face workers have a boil rate similar to that of workers elsewhere underground and surface workers, so one may conclude that colliers, rippers, and packers are the only men exceptionally at risk.

The Distribution of Boils

The relative frequency with which boils were distributed on different parts of the body was then related to the three broad occupational groups: coal-face workers, workers employed elsewhere below ground, and surface workers. The results of this analysis are shown in Fig. 1. (As some men reported with more than one boil the totals in this diagram exceed those in Table 2.) There are significant differences. The following conclusions may be drawn from the data presented in this figure.

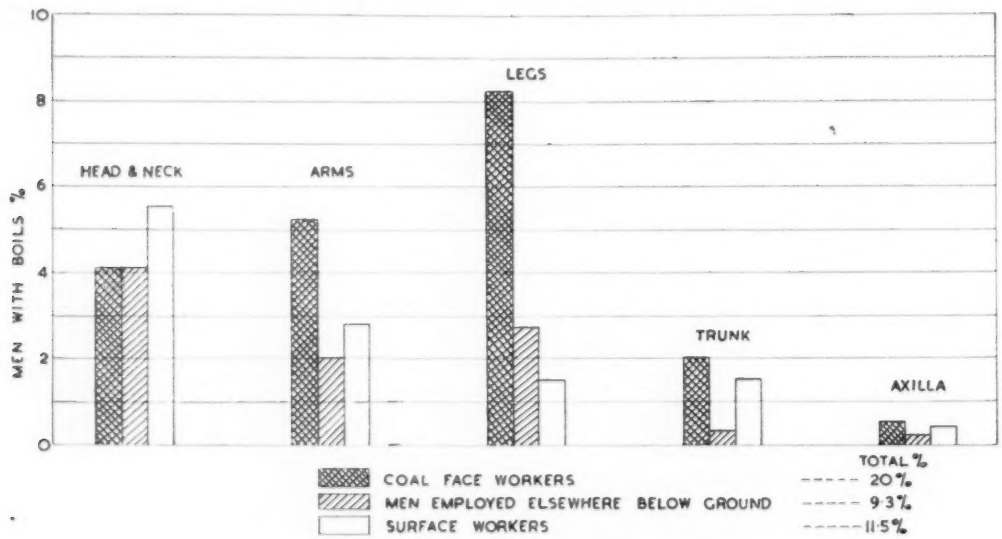

FIG. 1.—The incidence of boils by anatomical sites in the three occupational groups.

(1) The parts of the body most commonly affected are the head, neck, and limbs. (2) The incidence of boils on the head and neck is not very different in the three broad occupational groups. (3) Among face workers the limbs are more commonly affected by boils than the head and neck. This is in striking contrast to the findings in the other two occupational groups, where there is no substantial difference between the incidence of boils on the head and neck and on the limbs.

Recurrences

The recurrence rate was calculated for the three pits. The results are shown in Table 3.

TABLE 3
RECURRENCE RATE

Pit	No. of First Boils	No. of Recurrences	% of Recurrences to First Boils
A	194	74	38·1
B	193	62	32·1
C	219	95	43·4
Total	606	231	38·0

Miners who suffer from more than one recurrence, and many did so, were still regarded for the purpose of this analysis as suffering from one recurrence only. The difference in the recurrence rate between the three pits is not significant. However, the recurrence rate is quite substantial and brings the overall attack rate up to 17·7% for the three pits in the two-year period. It may be of interest to note that at Colliery A, where figures for time lost due to occupational disease were available for the period January to June, 1952, the shifts lost on account of boils per 100,000 manshifts worked were 196, which shows that boils among mineworkers are responsible for a significant loss in coal produced.

Relationship between Boil Rate and Environment

During the two-year period when this study was carried out, the boil rate on each face of the three pits, A, B, and C, was correlated with certain environmental observations, the ventilation rate and the dry and wet bulb temperatures. It was not possible to establish any consistent correlation between the boil rate and changes in the environment. Failure to establish a correlation may have been due to the fact that the observations were not made often enough or perhaps because the aetiology of furunculosis in the mining environment is more complex than has often been assumed. The immediate cause of boils is a pyogenic skin infection, but the predisposing causes may be excessive sweating, and mechanical and chemical trauma. Increased sweating does not by itself predispose to boils; indeed, in the spinning rooms of mills, where the atmospheric temperature is high, the workers sweat profusely, but from personal observations made in three mills they do not appear to be unduly troubled with boils. In contrast, face workers are constantly subjecting their knees and elbows to trauma. They push their shovels by pressing with knees and elbows, and the mechanical trauma is aggravated by dust particles. In certain places pit water has a high salt content, which may be a predisposing factor. Inability to obtain significant results from this part of the investigation should not discourage further efforts along these lines in future; indeed, it might be possible to establish a boil rate index as one biological criterion of the healthiness or otherwise of the mining environment.

Summary and Conclusions

A study of boils has been carried out over a two-year period at three pits at which a high incidence of this condition was reported. The boil rate over this period was 13·1% and, if recurrences be included, the overall attack was 17·7%.

Face workers were more commonly affected than workers employed elsewhere below ground and on the surface. Colliers and rippers suffered more from boils than packers and others. Face workers had more boils on the limbs than on the head and neck. The position was reversed for miners employed below ground other than on the face and for surface workers.

Owing to the complex aetiology of furunculosis, it has not been possible to establish a clear correlation between measurements of environmental data and the boil rates.

In the three pits which were studied, boils are responsible for a significant loss of production. It is possible that a similar loss of production occurs at other pits where the underground conditions approximate to those at the pits we have surveyed.

We are grateful to Dr. John Rogan, Chief Medical Officer, and Mr. R. C. Tomlinson, Statistician, Field Investigation Group, National Coal Board, for their invaluable help in preparing this paper. Acknowledgment is also made to Dr. J. Trefor Watkins, Divisional Medical Officer, East Midlands Division, the nursing officers and officials at the three pits concerned.

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INDIVIDUAL DIFFERENCES IN ACCIDENT SUSCEPTIBILITY AMONG COAL MINERS

BY

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From the Psychological Laboratory, University College, London

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DESCRIPTION AND SOURCE OF DATA

A system for recording and describing underground accidents was introduced at a group of collieries in the Nottinghamshire coalfield in April, 1944. Three months were spent in a trial period to eliminate working problems and to enable the foremen, safety-officers, labour department, and others concerned to become familiar with the system. The records proper began on July 1, 1944. At the same time, detailed working records were taken from one colliery in the group. These working records were produced weekly, and showed for each man his place(s) of work, his occupation(s), and the number of shifts worked in each occupation in each place. The data had been collected for the calculation of wages and cost analysis. In January, 1947, the costing classification was changed. This meant either working with the two-and-a-half-year observational period then complete, or attempting to match data from two classifications to use a longer period. The additional labour and possibility of error if the latter course were attempted probably would outweigh the increase in information gained from a longer period of study. Thus the data used in this investigation were obtained in the period July, 1944, to December, 1946, inclusive.

Working Environment and the Occupations

The colliery from which these records were taken is moderately large, having about 2,000 men on its books. The nearest village is about 1 mile away and is predominantly rural. Unlike many collieries it does not have a mining village of its own. The men come partly from the industrial areas of a large town, about 4 miles away, and partly from nearby villages. As the two seams worked are at moderate depth and both are dry, no temperature or humidity problems need be considered. The seams differ; one is hard coal, varying in thickness between 2 ft. 6 in. and 3 ft., with a firm stone floor and roof, requiring heavy props and bars. The other is a much softer coal, varying between 3 ft. 3 in. and 3 ft. 9 in., with a relatively soft and shaly roof. Both seams were worked (during the period concerned) on the longwall advancing method. The cycle of operations and the occupations involved may be briefly summarized.

The longwall or "face" of coal has three approaches ("gates"), one at each end and one in the middle. The face is first undercut from end to end to a predetermined depth by a cutting machine, operated by machinemen. At the same time the two conveyor belts (which run parallel to the face, one from each end to the middle) are dismantled and moved nearer to the face to be in position for the next loading shift. This movement of the conveyors is performed by flitters. The two belts converge on to a shorter belt, running at right-angles out towards the main roadway (the gate-end loader). This requires greater height than the seam itself allows, and also, it is placed in what will become part of the main road as the face advances. Gaining this extra height by digging into the "floor" and removing part of the "roof" is the work of rippers, who also install the girders of the roadways.

As the face is advancing at the rate of one machine cut per day, the space left behind after the coal has been removed is an important consideration. Near to the existing face this space is preserved by means of steel props and bars which prevent lowering or falls of the roof or the floor rising. (Under mining conditions earth can roughly be considered as a viscous fluid, and any disturbance will slowly be filled in from all sides.) Further back from the working space the steel props are replaced by "packs", mounds and walls of stone and rubble,

which give gently under the pressure of floor and roof. In due time these packs are compressed to the limit and the space previously occupied by coal has virtually ceased to exist. The rate of closure is important to the working of the face. If it proceeds too rapidly the strain on the roof may prove too great, causing major falls of roof. If too slowly, there is insufficient pressure on the coal at the face, and instead of the undercut coal being partially forced off the face by the roof pressure the full labour of prising it out of the solid is left to the collier. The men who build the packs and remove the props and bars are called packers.

After these preparatory operations the face is ready for the coal-getting shift. Shot holes are drilled by borers and charged and exploded by shotfirers. The coal is broken off the face, broken up, shovelled or lifted on to the conveyor belt by the collier. He also puts up the props and bars as he reaches the uncut coal behind. The coal goes along the conveyor, on to the gate-end loader and is tipped into the mine-cars (tubs), which have been manhandled into position by the loader. A train of tubs is coupled up, clipped on to the endless steel rope, unclipped and reclipped at junctions by haulage hands. At the bottom of the shaft they are unclipped, uncoupled, and put on to the cage (either by pushing, gravity, or mechanical aid) by the pit-bottom staff.

During the course of the investigation there was a steady change towards the use of main road conveyors instead of tubs. These main conveyors loaded into heavier mine cars near the pit bottom.

Work at the face is supervised, and the roof and propping examined, by the overman or his deputy. The main roads and haulage tracks are extended and kept in good condition by rippers and repairers. Maintenance and advancement of electrical equipment is the work of underground electricians. The few pit ponies which remain for odd haulage tasks are in the charge of horsekeepers.

Individual men work mainly at one occupation for some reasonable length of time, but intermittent changes are frequent, the overman booking his men to their jobs according to necessity. Temporary changes of working place are also frequent, and over the course of a few weeks a man may work at three or four occupations in as many or more working places.

Accident Records

The accident classification used for this investigation has subsequently been condensed and modified in some points to become the current Non-Fatal Accident Return Under Coal Mines Act (Ministry of Fuel and Power M.D. Return 39). The data are, therefore, presented in this latter form as an Appendix in Tables A, B, C, and D. The entries are for " compensation " accidents only. Nominally these are accidents which have prevented a man from earning his full wages at his normal work for a period of more than three days, but there are 4·2% of cases for which absence is reported as three days or less. These men may have returned to surface or light work only, or there may be errors in the records. Table I gives the median absence for different occupations.

TABLE I

NUMBER OF ACCIDENTS AND MEDIAN ABSENCE

Occupation	Accident Frequency	Median Absence
Colliers	562	10·5 days
Machinemen	94	9·5 ,,
Fitters	23	10·2 ,,
Packers	222	9·3 ,,
Loaders	49	8·8 ,,
Rippers, etc.	226	11·2 ,,
Haulage and pit-bottom staff	185	11·9 ,,
Overmen and others	48	13·7 ,,
All	1,409	10·6 ,,

COMPARISON OF INDIVIDUALS

To compare individuals on their accident experience it is necessary to have a common unit of measurement. For example, it is impossible to make direct comparison between a collier who has had three accidents in two and a half years and a haulage hand who has had one accident in two years. Some account has to be taken of the differences in objective or inherent risk between the two occupations. In the original studies of accident proneness by Greenwood and Woods (1919) this problem was avoided to a large extent by working with large groups of individuals who were assumed to be exposed to the same risk by virtue of the same number of days worked in the same occupation in the same factory building. To avoid complications caused by absence from work due to accident injury, only minor injuries, not involving absence, were studied.

This procedure raises some practical objections. The use of minor injury data can be criticized. An assumption that major and minor injury accidents are highly correlated in the sense that an individual who has a lot of minor accidents is also likely to have a lot of major accidents has not been verified. It seems likely that the correlation, though positive, is low. A more basic objection lies in the conclusion to be drawn when the Poisson distribution does not fit the data. " Proneness to report a minor injury " is as valid a conclusion as " proneness to

experience a minor injury '. This objection cannot be wholly overcome in any kind of survey. Whatever the definition of accident (except fatality), there is a margin within which the individual himself decides whether or not he has sustained an " accident ". If we take as " accidents " those occasions when absence from work is attributable to accident injury, the willingness or unwillingness of the individual to absent himself is a margin of error. For the main purpose of this study an " accident " was defined as an accident which resulted in injury sufficient to warrant compensation. To some extent the onus was, therefore, on the medical officers of the compensation department, working within the prescriptions of the Workmens Compensation Act. There is no doubt that some of the same type of variation persists, but this criterion was adopted as being perhaps the most standard and objective criterion possible under the circumstances. It has also the merit of being easily understood within industry, and the data can readily be collected as part of the existing requirements for the statutory returns.

As men in a coal-mine work in different occupations, in various parts of the colliery, and for varying periods, an assumption of equal risk over equal periods is untenable, and a comparative measure has to be found. For this, the risk per shift for moderately homogeneous working groups was found. Two main sources of heterogeneity were considered ; occupation and place of work. Although underground occupations are somewhat specialized it was possible to produce reasonably homogeneous occupation groups. Grouping was necessary for two reasons. Statistically the errors of small samples would outweigh the apparent increase in accuracy provided by fine divisions, and secondly there were enormous practical advantages to be gained by accepting existing classifications, even though these had been designed for other purposes.

The following occupation classification was used : (1) Colliers, including borers ; (2) machinemen ; (3) packers, flitters, loaders, rippers, repairers ; (4) haulage and pit-bottom staff ; (5) deputies, overmen, shotfirers, horsekeepers, underground electricians.

Groups 3 and 5 are the least homogeneous. Group 5 consists of a number of different occupations with comparatively few men in each. Group 3 includes more men, but the detailed classification of occupation in the accident returns did not match that of the cost analysis in any finer division.

Place of work was classified primarily into seam. In the case of colliers it was possible further to sub-divide into " districts ", either individual coal faces or two or three faces close together.

Given the number of accidents occurring in each occupation-place category, and the number of man-shifts for the same, it was possible to calculate the risk for that occupation in that place. This was done for all occupation-place categories, giving a series of risks per shift. It was then assumed that an individual's risk, for example as a machineman in No. 1 seam, was the number of shifts he had worked there as a machineman multiplied by the risk per shift for machinemen in No. 1 seam, established as described. Therefore, each man's working record for the period was taken, and the number of shifts he had worked as a collier in each place, as a machineman, as a packer or flitter, etc., were computed. From the rates per man-shift his risk in each category was determined. His total risk (i.e., his expected number of accidents) together with his actual accident history provides the basis for comparing him with other individuals.

There are some possible objections to this. It takes no account of change in risk due to change in working conditions over the period. It has also been shown that under certain conditions, such as length of shift, the simple arithmetical relationship between time and risk does not hold. This could possibly be true for longer time units, i.e., an individual who habitually works six shifts a week may be be exposing himself in comparison with an individual who consistently works five shifts more than a six-to-five ratio would indicate. To calculate this effect and allow for it would be very laborious. As it happens, in this study there is some evidence that individuals who sustain relatively many accidents work fewer shifts per week than the others. It is debatable whether an individual characteristic such as weekly working habit, or age, or experience should be taken into account at this stage, or whether they should instead be considered as possible factors making for individual difference in accident susceptibility.

A considerable number of men worked for short periods only during the observational period and, therefore, had only low total accident risks. This was in part due to the " Optant " and " Bevin Boy " schemes which were in force for part of the period. It was decided to exclude from further study all whose risk was lower than 0·300.* Table 2 shows the risk and accident distribution for the remainder.

The observed frequency of accidents in each

* This necessitated a slight modification of the calculated risk values.

TABLE 2

DISTRIBUTION OF ACCIDENTS AND RISK

Risk	No. of Individuals having Given No. of Accidents								
	0	1	2	3	4	5	6	7	8
0·300–0·499	141	74	20	9	1				
0·500–0·699	123	76	26	8	4	3	1		
0·700–0·899	127	76	39	20	8	1			
0·900–1·099	113	80	44	12	3	1	2		
1·100–1·299	50	31	31	5			1		
1·300–1·499	27	30	12	11	4		1	1	
1·500–1·699	27	30	17	7	4	1	1		1
1·700–1·899	22	14	3	5	3	2			
1·900–2·099	5	8	5	2	1	1			
2·100–2·299	3	1	1	1					
2·300–2·499	1								
2·500–2·699	1	1							
Total	640	421	198	80	28	9	6	1	1

risk group does not correspond to that expected on risk and number of men, although the totals agree with a small error attributable to grouping. Table 3 shows that this is a systematic discrepancy.

TABLE 3

SYSTEMATIC DISCREPANCY BETWEEN NUMBER OF ACCIDENTS EXPECTED AND OBSERVED*

Risk	No. of Individuals	Observed Accident Frequency	Expected Accident Frequency	Observed–Expected
0·300–0·499 ..	245	145	97·88	+47·12
0·500–0·699 ..	241	189	144·48	+44·52
0·700–0·899 ..	271	251	216·66	+34·34
0·900–1·099 ..	255	233	254·87	−21·87
1·100–1·299 ..	118	114	141·54	−27·54
1·300–1·499 ..	86	116	120·36	−4·36
1·500–1·699 ..	88	120	140·76	−20·76
1·700–1·899 ..	49	57	88·18	−31·18
1·900–2·099 ..	22	33	43·99	−10·99
2·100–2·299 ..	6	6	13·20	−7·20
Over 2·299 ..	3	1	7·60	−6·60
Totals ..	1,384	1,265	1,269·52	−4·52

* The small overall discrepancy is due to the grouping of the data.

Chi squared is 75·52, and with 11 degrees of freedom (as the grand totals do not agree exactly) this gives a probability of less than 0·0001.

The first hypothesis which must be considered to account for this is that if a man has an accident he is absent from work. His risk, based on the number of shifts worked, will be lower than that of an otherwise comparable man who has not had an accident. Therefore, it might be thought that those men who had many accidents would " drift " down into the lower risk categories by virtue solely of their absence. If the absence were long enough this would certainly produce the effect noticed. But this does not seem to be the case. The median absence per accident for the groups of risk 0·300–0·499 and 0·500–0·699 is 10·9 days. This corresponds approximately to an arithmetical average of 13·9 working days. This loss of working days would correspond to a reduction of calculated risk by 0·0467 per accident in the case of colliers, who have a relatively high risk. Thus in the 0·300–0·499 risk group a total expectation of 6·77 accidents may be considered lost in this way. As the actual discrepancy is 47·12, some other cause must be assumed to operate. In addition, the effect is actually overestimated in this simple approach ; it cannot be assumed that had there been no absence there would have been no additional accident during the period.

A second possibility is that the low-risk groups contain a higher proportion of individuals who first began underground work during the observational period, and that the discrepancy is due to their inexperience. This is not borne out by the relationship of age to accident history ; the younger men, a large proportion of whom are new to the industry, do not show such an increase in incidence over expectation.

A third hypothesis is that there is a relationship between accident proneness and attendance at work. The working records for a period of 20 weeks were studied for three samples of men. The samples were extracted for the observations described in the detailed study of selected individuals and consist of (+) men who had many more accidents than their calculated risk ; (=) men who had approximately the same accident history as their calculated risk ; (−) men with no, or at most one, accident and a high calculated risk. For this attendance study the full samples were used, except for one (−) individual who was absent for the whole of the 20-week period (Table 4).

TABLE 4

DISTRIBUTION OF SHIFTS WORKED PER WEEK IN THREE SAMPLES* (in %)

No. of Shifts Worked in Week	(+)	(=)	(−)
0	10·78	3·06	2·93
1	2·19	0·81	0·69
2	2·66	1·94	2·07
3	9·84	6·45	5·69
4	15·78	13·55	12·93
5	23·91	28·87	22·41
6	30·62	32·58	38·79
7	3·91	10·48	10·52
8	0·31	2·26	3·97
Mean number of shifts worked in week	4·33	5·10	5·24

* 20-week period February 1–June 21, 1946.

The (+) group worked significantly fewer shifts per week than the others. There is the possibility that this is an artifact of the sampling procedure. The (−) group, in particular, is drawn from men who have a high calculated risk and who, therefore, must have worked a great deal. But this is not

necessarily true of the (=) group. The (+) group comes from men with a low calculated risk, who must have worked less than most during the observational period. But if this were due to accident absence, or to having begun underground work during the observational period, then while they were available for work there should be no difference between them and the others in respect of attendance. If it can be taken, as is intended, that the (+) group is a representative sample of accident-prone individuals, a general relationship between accident proneness and short-week working can be suggested. The problem will be discussed later on.

Although the term "accident-proneness" has been introduced, it is not very easy to demonstrate its existence in a clear-cut statistical fashion. The systematic discrepancy between the expectation based on risk, and the observed accident frequency discussed above means a choice of assumptions on which chance distributions are to be based. Three chance distributions have been calculated and χ^2 tests of goodness of fit applied. The distributions are: (*a*) Poisson distributions based on mean calculated risk in each risk group. (*b*) Poisson distributions based on actual mean accident rate for each risk group. The assumption, therefore, is that the systematic discrepancy is evenly distributed amongst individuals, and that the observed means are true measures of risk. (*c*) Yule's negative binomial, based on observed means and variances.

It will be seen that (*a*) does not fit at all, (*b*) is slightly better, and that (*c*) fits quite well, the only odd value occurring in the 1·1–1·299 risk group (Table 5). (Fuller tables are available on application to the author.)

Thus we can say that even within the risk groups and even eliminating the overall discrepancy from consideration, an assumption of equal liability amongst individuals does not hold. The conclusions from the comparison of individuals are therefore: (1) There are more multi-accident individuals than would be expected on the assumption of equal liability. (2) These multi-accident individuals tend to have been exposed to a comparatively low risk of accident. The evidence is suggestive that they are irregular in their attendance at work.

THE RELATION OF AGE TO ACCIDENT RISK

The data were analysed into five-year age groups, within each of which the total number of accidents and the total calculated risk were found for each of the occupation groups. These are shown in Table 6.

In considering these observations two points must be borne in mind. The first is that differences in age may be related to differences in actual work. This is particularly to be expected in team occupations, where the youngest are probably acting as assistants, those somewhat older taking the main burden, and the older men directing and supervising the work. The second is concerned with selection effects. The older men in the more strenuous occupations are generally the more physically fit members of their age group. These points make it difficult to generalize about the relation of age to accident

TABLE 5
χ^2 VALUES OF GOODNESS OF FIT OF THREE DISTRIBUTIONS

Calculated Risk Group	(a)			(b)			(c)		
	χ^2	d.f.	P	χ^2	d.f.	P	χ^2	d.f.	P
0·3–	18·97	2	0·0001	5·16	2	0·1	0·61	1	0·4
0·5–	20·09	3	0·001	6·72	2	0·05	2·99	1	0·08
0·7–	25·44	3	0·0001	16·69	2	0·001	2·02	1	0·16
0·9–	6·43	3	0·1	3·22	2	0·2	1·70	1	0·19
1·1–	14·90	3	0·01	9·78	2	0·01	10·43	1	0·0013
1·3–	5·80	3	0·2	5·42	2	0·1	1·94	1	0·16
1·5–	7·67	3	0·1	1·65	2	0·5	1·16	1	0·28
1·7–	32·46	3	0·0001	12·62	2	0·01	3·67	1	0·06
1·9–	9·26	2	0·01	1·69	2	0·5	0·01	1	0·91
Totals	141·02	25	0·0001	62·95	18	0·0001	24·53	9	0·01

TABLE 6
OBSERVED AND EXPECTED NUMBER OF ACCIDENTS BY AGE

Age on 1.1.46	Colliers		Machine-men		Rippers, etc.		Haulage		Overmen, etc.	
	O	E	O	E	O	E	O	E	O	E
–22	113	107·4	2	6·1	41	77·9	55	40·6	1	5·0
23–27	66	56·5	8	8·8	25	25·9	11	14·5	2	3·9
28–32	42	44·5	9	6·8	24	28·8	10	8·3	2	2·4
33–37	49	54·5	5	7·7	59	49·2	15	14·1	3	5·5
38–42	93	94·5	34	26·3	108	90·3	16	20·7	3	4·8
43–47	65	77·9	17	24·2	50	55·3	9	10·6	15	10·0
48–52	63	57·0	2	1·3	59	44·4	8	13·7	7	6·0
53–57	22	23·3	5	3·4	50	34·6	9	7·5	6	3·4
58+	19	15·8	7	4·6	42	51·5	8	11·1	6	4·9
Totals	532	531·4	89	89·2	458	457·9	141	141·1	45	45·9

O = Observed frequency. E = Expected frequency.

susceptibility and the observations are descriptive only.

The relationship may be studied in each occupation. For colliers there is little evidence of any relationship, except for a slight superfluity of observed accidents with the young and the old. In actual practice it is likely that the difference in real risk is considerably more than is shown here, for two reasons, both concerned with the working arrangements of the colliery. Young men are trained as colliers on special training faces until they are judged competent for normal face work. On these training faces the amount of coal to be loaded is less than on the full working face, and only the fit men proceed rapidly through the training faces to full work. Thus both environment and selection are at work to reduce the risk of the younger men. Up to a point the environmental difference is taken care of in the calculation of risk. (Individual faces were used where possible to provide the basis for the calculation of colliers' risk.) At these training faces a number of older men are also employed, particularly the steady workers whose example of good working method is valuable instruction for the trainees. And as only the fit older men continue to work as colliers, it would appear also likely that the effect of age on accident liability is obscured for the older men as well. These points, or their presumed effects, are conjecture, but it seems possible that in the statistically ideal condition of equal sampling and objectively equal exposure the effects of inexperience and age would be much more marked.

Machinemen work as a team, and the relation of age to accident liability is most likely to be derived from the relationship of age to specific occupation in the team.

As mentioned earlier, the rippers, repairers, etc., group is not very homogeneous. Age is likely to be related to actual differences in work.

Haulage involves a lot of very young and inexperienced men, and the less fit members of other age groups. As far as the younger men are concerned, it is usually their first occupation underground, and it is reasonable to suggest that their relatively high accident incidence is due to inexperience, to the specific nature of their work, and also to general conditions underground.

FAMILY RELATIONSHIP AND ACCIDENT RISK

Mining is still to some extent a family occupation. At this colliery there were a number of family groups working. Two relationships were studied: father and son, and brothers.

There were 50 fathers with a total of 61 sons working in the mine. To obtain a comparative measure the following transformation was adopted. Each individual was given a percentile rank as to his standing on accident history related to his exposure. A Poisson distribution of accidents was assumed; e.g., if an individual had one accident and a calculated risk of 0·800, we would expect 19% of the population to have more than one accident with this risk, and 36% to have one accident only. Thus the percentile standing of this individual is 19 + 18 = 37, which is the percentage of the population expected to be worse than he is.

There is little overall relationship, but a breakdown of the data in Table 7 shows that accident-free fathers tend to have accident-free sons.

TABLE 7
ACCIDENT LIABILITY OF FATHERS AND SONS

Percentile Grade of Father	No. of Fathers in Grade	Mean Grade of Sons of these Fathers	No. of Sons
0–24	14	45·33	21
25–74	23	52·71	24
75–99	13	66·50	16

There were 86 families of brothers comprising 189 individuals. There was no relationship in accident liability.

These samples are incomplete if we wish to consider the possibility that differences in accident liability are inherited. Some sons or brothers may have left the industry, or may be working in other collieries. It is possible that such self-selection might be related to accident proneness. A man whose father is accident prone may decide more readily against working in a mine than one whose father is comparatively free from accident. This does not seem likely from the sample, as the relatively accident-prone fathers have the highest proportion of sons in the mine. From the point of view of simple inheritance we would expect a similar relationship to exist between brothers as between fathers and sons, and it is not easy to see how any selection effect could alter one relationship without disturbing the other. As the only significant relationship is that the sons of the 75–99 percentile fathers are freer from accidents than the others (Student t = 2·22), it would appear more likely that the accident-free fathers train their sons in good working practices, either directly or by advice and explanation.

DETAILED STUDY OF SELECTED INDIVIDUALS

Studies of the personal qualities associated with accident proneness have usually taken the form of measurement or appraisal, over a large sample,

of those qualities considered relevant. The measures have then been correlated with subsequent accident histories. This method has two valuable characteristics; (1) it is concerned with predisposition, and post-accident effects can be disregarded, and (2) assuming the sample to be random for the population in or entering the industry, the degree of relationship shown between the qualities and accident proneness can be considered as measured for the relevant population as a whole. At the same time this method has a major disadvantage. A large sample is required, partly because of the Poisson-like distribution of accidents, and partly to cover loss through retirement or change of work during the follow-up period. A large sample imposes severe practical limitations on the amount of information it is possible to obtain about each individual.

An alternative approach was used in this investigation. Three comparatively small samples of men were chosen on a basis of their known accident history. The observation period was the two-and-a-half year period referred to earlier. One sample was composed of men who had experienced many more accidents than their calculated risk warranted. These are called the (+) or accident-prone group. Each individual in this group was matched with two other men in respect of age and normal mining occupation. In a few cases the matching is approximate only. These two other men represented two other types of accident experience. One had experienced about as many accidents as would be expected from his calculated risk, an accident-average or (=) man, the other had been remarkably free from accident, and accident-free or (−) man. One triad may serve as an example.

The triads were examined by Dr. D. Russell Davis, Dr. R. B. Buzzard, Mr. I. Gordon Brown, Mr. H. Letty, Mr. J. Spencer, and myself (I wish here to express my indebtedness to my colleagues). Dr. Russell Davis's special interests in the investigation have been published (1949). The members of the team were aware that each triad consisted of a (+), (=), and (−) individual but, with the exception of myself, they did not know which was which. To maintain this freedom from bias I confined myself to those measurements which were free from subjective judgment.

Thirty-three triads were arranged, the first to act purely as a trial run for testing the experimental procedures and timing the programme. The remaining 32 triads divided themselves fairly conveniently into four age groups. The age is given as at January 1, 1948.

Group	No. of Triads	Range of Average Age	Individual Age Range
A	7	22–25	27–20
B	12	34–44	45–33
C	8	47–50	51–42
D	5	55–64	66–53

The overlap in individual ages between B and C is confined to two cases, one each way, and is caused by the difficulty of matching occupations as well as ages.

Six subjects did not appear, leaving a total of 90 individuals. The failures were: (1) (+), age group D, (2) (=), age groups A and B, (3) (−), two age group A and one age group C. The standing of the samples on a Poisson percentile, calculated as on page 131 is shown in Table 8:

TABLE 8

MEAN PERCENTILE STANDING OF SAMPLES

Group	(+)	(=)	(−)
A	7·0	51·8	86·2
B	2·6	48·0	86·3
C	2·8	48·9	87·3
D	9·0	50·0	88·6

Thus the samples can be held to represent the extremes and the middle of the population from which they were drawn.

As the observational period was relatively brief, and in view of the suggestion by Johnson and Cobb (1938) and Johnson (1946) that there is comparatively little correlation in accident proneness over successive observation periods, it seemed necessary to consider whether these samples were representative in a wider sense, i.e., that the accident-prone individuals were persistently so and not merely individuals who had " struck a bad patch "

Triad No.	Accident Class	Year of Birth	Expected No. of Accidents (by occupation groups)						Accidents					
			C	M	PR	H	O	Total	C	M	PR	H	O	Total
	+	1924	0·604	0·020				0·624	5					5
2	=	1927	1·041	0·011	0·156	0·098	0·001	1·307				1		1
.	−	1925	0·944		0·092	0·087		1·123						0

C = collier, M = machineman, PR = packer and ripper, H = haulage hand, O = overman.

coincidental with the period of observation. A *post hoc* enquiry was made a year after the investigation. The records could not be treated in detail in that calculated risk could not be measured in any real sense. A few individuals had left the colliery and their records were not available. Taking as a crude measure accident rate per month of exposure (neglecting actual attendance or occupation, although the latter can be assumed to be fairly well balanced for the samples) the following was observed (Table 9).

TABLE 9

ACCIDENT RATES PER MONTH FOR SAMPLES BEFORE AND AFTER OBSERVATION PERIOD

	1938 and 1939	1940 and 1941	1942 and 1943	1944 (to 30·6) and 1947	All
(+)	0·0263	0·0470	0·0593	0·0472	0·0458
(=)	0·0175	0·0280	0·0500	0·0261	0·0315
(−)	0·0100	0·0270	0·0297	0·0292	0·0238

The overall differences are significant. As they are based on very crude measures they imply that the samples chosen are representative for a period considerably greater than the observational period.

Measures Used and Design of the Investigation

No overriding theory governed the selection of measures used in this enquiry. As the number of individuals studied was small, and the time available with each correspondingly large (about five hours), it was felt that all measures could be used which might reasonably be assumed to relate to the problem on psychological grounds, although the previous work by Farmer, Chambers, and Kirk (1933) to some extent dominated the choice of measures. Some measures which might have proved desirable, such as a standard intelligence test, were omitted on practical grounds. The measures used fall into the following groups.

Acuities.—A miner works in dim illumination, and often with a background of considerable noise. (It is commonly held that changes in the creaking of the roof and supports are an important sign of danger from falls of roof.) Therefore, visual and auditory acuities were measured. Visual acuity was measured by Snellen cards, four of which were used, the first presented in daylight, the others presented after five, 15, and 30 minutes of adaptation to dim light, approximately that cast by an ordinary miner's lamp. Differential auditory acuity was measured by subjecting the individual to a fixed intensity of sound, and introducing known intensities of sound of different frequency. (The apparatus was designed and built by Dr. A. Carpenter.)

Medical History and Present Medical State.—This was aimed at determining the extent to which physical or medical disability was responsible for accident proneness.

Interview.—The interview was concerned with the attitude to work, domestic and other environmental circumstances, and an assessment of the amount and direction of the individual's activity.

The medical and interview data proved to be valuable background material, but except for a few specific instances it was not possible adequately to codify them into any reasonable statistical classification. However, as the number of individuals studied was small the various details thrown up from these sources were valuable, in retrospect, to the members of the team, and contributed greatly to the interpretation of the more easily systematized data.

Performance Tests of Perceptual, Cognitive, and Memory Functions.—Test 28, originally devised by Bartlett, involves mainly spatial perception and memory.

Test 28.—A display is given with four columns and seven rows with a symbol, word, or representative drawing in each cell. It is shown for 30 seconds and then replaced by a similar display in which some of the symbols, etc., have changed position. The subject enters on a proforma whether in each cell the entry is the same as before, different, in the sense that the symbol was previously somewhere else in the display, or whether the symbol is a new one altogether. There is a time limit of two minutes. The second display is then removed and the subject enters on a second proforma the entries cell by cell for the original display (two minutes' time limit). Scoring is the number correct in both cases.

The Rey-Davis Test.—This has been described by Zangwill (1946). Four squares of wood, each with nine knobs, are arranged to form a large square. In each small square one knob is free to move, the others are fixed. The subject begins at the top left small square and discovers by trial and error which is the free knob. He then goes to the next square clockwise and does the same, continuing round and round until he has learned which is the free knob in each square (five consecutive correct trials being the criterion of learning). The whole square is then rotated ninety degrees clockwise and the subject relearns. The number of errors is taken as the score.

Matching.—This test was devised for the investigation. It consists of six photographs of underground mining operations. These were cut into two, along the N.E.–S.W. diagonal. To make matching less a process of immediate perception, and more a task involving judgment and interpretation of the material, a strip of the photograph along the diagonal was obscured. This provided a gap, which the subject had mentally to jump in his perception. The top portions were fixed on a large sheet, and the six bottom parts were shuffled and handed to the subject A specimen photograph (not one of the six) was demonstrated to the subject to show him how the pieces matched and to draw his attention to clues provided by continuity of scene over the gap. The subject was then asked to match the six bottom pieces against their appropriate tops, two minutes being allowed. They were then shown which matches were correct and which

incorrect, appropriately marked cards being placed against the photographs as well as verbal indication given. The subject was allowed to look at this without manipulating it in any way for half a minute. The bottom pieces were removed, shuffled, and the subject made a second attempt, one and a half minutes being allowed. The procedure was repeated for four trials or until perfect matching was obtained. Scoring was on the basis of information gained (Whitfield, 1951).

Directions Test.—Ten directions test questions were read to the subjects, with one minute in which to write the answer to each. This test was not standardized until the tenth triad.

Motor Control and Coordination.—Two performance tests were used.

Craik Triple Tester.—This is a tracking task; the subject uses a wheel to control the position of a pointer, with the aim of making as many contacts with irregular dots on a moving display as possible. Two conditions were used, one with little foreknowledge of the track ahead, and the other with greater visibility ahead but an indirect velocity control through an integrating disc. One preliminary trial was allowed in each condition.

Davis Controlled Response Test (Davis, 1949).—The subject controls a pointer through a velocity control actuated by a wheel at the subject's left hand. The pointer has to be moved to the central, left, or right settings on the receipt of light signals. In some instances the signals are ambiguous. A continuous record of wheel movement is made. Several quantitative measures were attempted (reaction time, extent of movement, overshooting, undershooting, reversals, etc.), but it was discovered that they did not adequately describe the differences between the records. The complete traces were then rated on overall performance by an assessor, who was kept unaware of the identity of each record.

Statistical Treatment of Data*

Some of the data were expressed in quantitative terms (e.g., number of contacts made with the triple tester), some as ratings (as in the interview and the controlled response test), and some as order of merit. The quantitative measures cannot be assumed to be distributed normally. It is obviously convenient to use a single measure of relationship throughout, and so all measures were expressed as order of merit. The best performance is ranked 1, the worst 90. The relation between performance and accident proneness is expressed as a Kendall τ correlation, comparing the ranks assigned to the (+) with those assigned to the (=) and (−) groups combined. Hence a positive value means that the (+) group performed better than the others. In each case the significance is tested as described by Whitfield (1947). It is worth mentioning that τ is numerically smaller than the equivalent product moment correlation, but a product moment correlation would not be valid for samples of this nature.

* Full details of observations are available on request.

Where the observations permitted good discrimination (as in the performance tests) the data were analysed separately for the four age groups. Where the measures were relatively crude classifications (as in the interview and medical data) the age groups were condensed into (A + B) and (C + D). The correlations are given in Table 10. The probability values quoted are for the magnitude of the correlation, irrespective of sign.

TABLE 10
SUMMARY OF CORRELATION VALUES COMPARING ACCIDENT GROUP WITH OTHERS

Measure	Age Group	Accident Group
Visual acuity	A	−0·211
	B	0·183*
	C	0·485 (P = ·030)
	D	0·073
Auditory acuity	A	−0·061
	B	−0·147
	C	0·266
	D	0·555 (P = ·044)
Medical history: Presence of significant disease	A + B	0·091
	C + D	0·187
Tempo (normal/disturbed)	A + B	−0·101
	C + D	−0·008
Reflexes (normal/disturbed)	A + B	−0·157
	C + D	−0·072
Stated weight (heavy/light to nearest half-stone)	A	0·533 (P = ·020)
	B	0·341 (P = ·033)
	C	−0·051
	D	−0·035
Physique	A + B	0·401 (P = ·002)
	C + D	−0·124
Attitude to health	A + B	−0·033
	C + D	0·190
Mobility	A + B	−0·138
	C + D	0·056
Interview data: Adversity of circumstances	A + B	−0·303 (P = ·038)
	C + D	−0·011
Breadth of interest	A + B	0·263
	C + D	0·226
Total activity	A + B	0·213
	C + D	0·147
Directions test	A + B	−0·312 (P = ·043)
	C + D	0·100
Visual-cognitive tests (total rank order)	A	−0·452 (P = ·030)
	B	−0·415 (P = ·004)
	C	0·368 (P = ·042)
	D	−0·032
Motor control and coordination tests (total rank order)	A	0·046
	B	−0·158
	C	−0·449 (P = ·013)
	D	−0·232

* A positive value means that the accident group performed better than the non-accident groups.

Results of Observations and Tests

Acuities.—These show little relationship with accident proneness and the slight indication is contrary to expectation. This does not mean that defect of vision or hearing is necessarily without effect, but it does imply that variation of acuity within the normal (sample) range is of no predictive value for accident proneness. Two cases only of gross defect were observed. One with markedly poor vision was a collier, aged 50 at the time of the investigation and with an accident-free history. The other was a packer and ripper, aged 25, accident average, who suffered from middle-ear defect.

Medical History and Present Medical State.—As mentioned earlier, this largely provided background information, not easily expressible in quantitative terms. The two significant relationships observed are unexpected and interesting. The younger accident-prone men (groups A and B) are heavier than their contemporaries and were judged to be of superior physique.

One case of gross restriction of movement was observed, a collier aged 52, whose right elbow articulation was restricted to about 30 degrees, as a result of a childhood fracture being badly set. He was in the accident-average category, and it is interesting to consider that in spite of this severe restriction of movement he should have proved able to cope with the heavy lifting and shovelling work for so long. One marked post-accident disability case was discovered. A packer-ripper, aged 58, had, before the observation period, received severe head injuries, with considerable loss of intellectual function. The clinical picture was somewhat confused by chronic alcoholism. This man was free from accident during the observational period, but there is some justification for suspecting that this was due to comparative inaction.

Interview Data.—Again this mainly provided background material; the specific questions for the interviewer's judgment did not show much relationship with accident proneness, with the exception of "adversity of circumstances". Younger accident-prone men show greater adversity, judged by their accounts of upbringing, early life, and present state.

Perceptual-Cognitive Tests.—These show a well-marked relationship. Younger accident-prone men are markedly deficient in these groups of measures (with which we can associate the Direction Test). Older accident-prone men show no such deficiency; in the C age group they show significant superiority.

Motor Control and Coordination.—There is little relationship in the younger age group with these measures, but the older accident-prone are markedly deficient.

Thus overall it appears that accident proneness is related to the measures in the following way. Younger accident-prone men tend to be heavy, with powerful physique, with little or no impairment of motor control or coordination, but they give markedly poor performances on tests involving perceptual, memory, and cognitive processes.

Older accident-prone men are average or above average in the perceptual and cognitive tasks, but considerably inferior in motor control and coordination.

DISCUSSION

It seems fairly clear from the survey data that there exist individual differences in accident susceptibility amongst coal miners. Further, it appears that these statistical differences cannot readily be attributable to differences in age, and the study of family relationship does not suggest any simple form of inheritance. The main bulk of the evidence on the nature of accident proneness comes from the study of the selected samples. It now remains to consider whether this evidence can be put together to form a coherent picture of accident proneness, from which specific and testable hypotheses may be drawn.

If an accident is considered as a failure to make an adequate response to a hazardous situation, such failure could arise from failure in either or both of two constituent processes. There may be (*a*) failure to appreciate the demands of the situation, a failure of the individual to perceive the hazard or to decide what, if any, response ought to be made, or (*b*) there may be failure adequately to produce the appropriate response, even though the hazard has been perceived and an appropriate course of action initiated. The accident-prone individual may, therefore, be considered as an individual who habitually fails in either or both of these respects.

The two sources of failure, (*a*) appreciation and (*b*) performance, can be expected to be demonstrated in the two groups of psychological tests used. Failures of appreciation ought to be shown in poor scores on the visual-cognitive group of tests and performance failures in poor scores on the motor control and coordination tests. The observations in this study agree with this; the accident-prone individuals give poor scores on one or the other of the test groups. There is also a strong indication that the type of failure associated with accident proneness differs with age. Putting the conclusions in their simplest form, young accident-prone men show failure of a perceptual and cognitive nature, without any defect in the response mechanism; older accident-prone men show failure to produce an adequate response, although it appears likely that their perceptual and cognitive ability is normal.

This raises a new problem and there are several choices of argument. One possibility is that both types of accident proneness exist independently of age, and that the observed age difference is a sampling artifact. This could come about by means of a change in the type of person recruited to the industry over the past 30 years. Or, alternatively,

the type of accident-prone person characteristic of the younger age groups may leave the industry, thus allowing only the other type of accident proneness to be demonstrated in the older age groups. These are possibilities which cannot be excluded completely. The second could be verified by a study of "leavers", particularly those with a multi-accident history, and by studying the early accident histories of the known older accident prone.

But if the sampling possibilities are discounted there still remains a major choice of argument. Either accident proneness is not a persistent characteristic of the individual, or else the perceptual, cognitive, and motor abilities measured in the enquiry are not relatively stable, in the sense that an individual does not maintain his position with respect to his contemporaries. It is usually considered that these performance measures are moderately stable for the individual, and failing direct evidence the remainder of the argument is based on the assumption that they are This view is somewhat strengthened by the data on weight and physique, where there are marked differences between the younger and older accident-prone men.

One feature common to both young and old accident prone, and which is possibly a counter argument against this assumption, is their working fewer shifts in a sample period than the others. While this is a common feature if overall averages are used, an alternative measure of number of weeks with the full six shifts or more shows that the younger men work significantly fewer such weeks, whereas the older men do not differ significantly. The difference, however, is not very great, and it appears that short-time working is a feature of accident proneness *per se* rather than the prerogative of one of the postulated types.

Let us consider first the older accident prone, the man who has normal or good perceptual and cognitive ability, but whose motor control is below normal. As a young man he was probably able to cope with most situations, his anticipation of events enabling him to respond well within the limits of his motor ability. As he grows older, slowly his motor ability deteriorates (not necessarily more rapidly than in other individuals), his reaction time increases. There may also be some deterioration in perceptual and cognitive ability. The stage is reached when an appreciable number of situations, with which he previously could have coped adequately are now just about the limit or beyond the limit of his combined perceptual and motor ability. This is likely to be a slow process, and it is not likely that he is aware of it, or sufficiently aware to modify his working behaviour. It is more likely that he persists in his usual work and usual methods of work and becomes accident prone without knowing anything about such change. It may be suggested that this process might account for the observation, frequently made by factory and mine managements, that some of the safest men might get killed.

The converse problem, why the younger accident-prone men apparently cease to be so, is less easy to explain. It may be that they leave the industry—as is suggested above. However, some of the test evidence suggests a similarity between the young accident prone and the older accident free. *Post-hoc* discussion with the interviewer gave rise to the observation that some of the older accident-free men "looked like young accident-prone men who had worn themselves out". This is very slender evidence, but it is perhaps worth speculating that the active carelessness (lack of foresight, appreciation of the situation, etc.), characteristic of the young accident prone can be replaced by a passive carelessness. Some of the older accident-free men gave the impression at interview that they were accident free largely by virtue of decreased activity and hence decreased risk, unassessable in terms of shifts worked. The suggestion of a change from active to passive carelessness is unverified, and is not a satisfactory psychological description. Much more evidence is needed, first to demonstrate whether such a change takes place, and secondly to define the process in more acceptable psychological terms.

Failing such evidence, the observations can only be expressed as hypotheses, which can be restated: (i) Accident proneness is a behavioural symptom of either (*a*) deficiency of perceptual or cognitive ability, or (*b*) deficiency in motor ability. (ii) These deficiencies become apparent in accident proneness at different ages. Perceptual and cognitive deficiency makes itself shown with younger men, and motor ability deficiency in older men. (iii) Perceptual and cognitive deficiency, if associated with marked activity, are shown in accident proneness; but reduced activity may give a spurious indication of accident safeness. (iv) The individual who is deficient in motor ability compensates for this by anticipation, but this compensation is of steadily decreasing adequacy as age increases.

CONCLUSIONS

The conclusions drawn from one experiment only may not be valid, and the primary hypotheses developed in this study should be tested. Samples of accident-prone individuals of different ages should be examined to see whether the relationships

indicated are capable of generalization. Such an investigation should aim at closer delimitation of the age range in which the transition between the two types of accident proneness takes place. If the transition is demonstrated, and its age range measured, the next stage would be to study more closely the development of the "older type" of accident proneness. The practical aim would be to determine methods whereby the older accident-prone man could be detected sufficiently early and protected. The social loss caused by injury to the older men is very great, both in terms of their domestic commitments, which are probably greater and less flexible than those of younger men, and also from the point of view of the industry in respect of the wide mining skill they have attained.

The problem of the younger accident prone is more difficult. If, as the interview data suggest, adversity of circumstances, particularly in youth, is a predisposing quality, this is not susceptible to direct action by the industry. Nor would their rejection by the industry be satisfactory policy. It would seem that the only way of tackling the problem is by training. It may be impossible to teach caution to a happy-go-lucky, careless person, but specific working methods, appropriate to their lack of foresight, could be worked out and taught. An awareness of safety officers and instructors that good motor co-ordination is not, by itself, an indication of freedom from accident risk would be of value to this end.

SUMMARY

Disabling accidents were studied at one colliery from July 1, 1944, to December 31, 1946. Individuals who worked for brief periods only were excluded, leaving 1,384 miners with 1,265 accidents. An actuarial risk was calculated for each man, based on the number of shifts worked, place of work, and occupation. Discrepancies between calculated risk and actual accident experience were analysed, and accident proneness demonstrated.

Accident proneness was related to age, family relationship, and physical and psychological characteristics. Differences were found between the younger and older accident prone; in particular, the younger accident prone showed deficiencies in perception and cognition, whereas the older accident prone were deficient in motor response performance.

This work would not have been possible without the help of many people. In addition to those who took part in the study of individual cases, the writer wishes to thank Mr. E. Farmer, Reader in Industrial Psychology in the University of Cambridge; Mrs. D. Collins, of the Applied Psychology Research Unit, Cambridge; the management and staff of B.A. Collieries, Ltd., particularly Mr. O. B. Lewis and Mr. G. P. Thompson, and the men who subjected themselves to examination. The writer also wishes to thank the Medical Research Council for their support, and Professor Sir Frederic Bartlett for his constant encouragement.

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[*Appendix overleaf*]

APPENDIX

TABLE A

ACCIDENTS CLASSIFIED IN OCCUPATIONS* AND OPERATIONS

	C	M	F	P	L	R	H	O	Total
A1. Using pick, shovel, ringer, hammer	214	17	2	13	5	83	3	1	338
A2. Using other hand tools	1	—	—	1	—	—	—	—	2
A3. Collecting hand tools or appliances	2	—	—	1	—	2	—	—	5
A4. Building packs	—	—	—	54	—	7	—	1	62
A5. Erecting scaffolding	—	—	—	—	—	1	—	—	1
A6. Setting or withdrawing props, bars, or girders	62	3	9	88	2	31	6	3	204
A7. Laying or repairing haulage track	—	1	—	—	—	2	5	—	8
A8. Loading by hand on to face conveyor	24	—	—	—	1	5	—	1	31
B1. Driving or servicing cutter machine	3	46	2	—	1	—	1	1	54
B2. Driving or servicing power loader	—	—	—	—	—	—	1	1	2
B3. Servicing or moving conveyor	7	—	5	8	7	3	3	3	36
B4. Loading from gate-end or main loader	—	—	—	—	7	—	5	—	12
B5. Using boring machine	3	1	—	—	—	3	—	2	9
C1. Attending pump or fan machine	—	—	—	—	—	1	—	—	1
C3. Repairing power machine or cable	—	—	—	—	—	—	—	1	1
D1. Coupling or uncoupling tubs	—	—	—	2	—	1	23	—	26
D2. Attaching or detaching tubs	1	—	1	—	1	3	28	—	34
D3. Lockering or spragging	1	—	—	—	1	1	14	—	17
D4. Pushing tubs on or off cage	—	—	—	—	—	—	3	—	3
D5. Otherwise handling tubs	—	—	—	—	7	6	44	2	59
E1. Travelling or manriding underground	27	4	1	12	3	14	5	13	79
E3. Charging shotholes or firing explosives	—	—	—	—	—	—	—	5	5
E4. Sheltering from shots	9	1	—	2	—	—	—	1	13
E6. Loading and unloading stores and moving material	30	3	1	10	3	22	14	—	83
E8. Cleaning up, stonedusting, whitewashing	—	—	—	—	—	1	—	1	2
J1. Supervision or inspection	—	—	—	—	—	—	—	3	3
J4. Any other operation	—	—	—	—	—	2	—	1	3
Insufficient detail reported	178	18	2	31	11	38	30	8	316
Total	562	94	23	222	49	226	185	48	1,409

The occupation is that for which the man was booked on the day of the accident, and does not take into account the odd half hour changes of work which sometimes happen, e.g., a haulage hand would not normally be driving or servicing a cutter machine, but one may have been available when an extra man was required, and in so working he received an injury.

TABLE B

OBJECTS INVOLVED AND INTERVENING CAUSES

Object Involved	C	M	F	P	L	R	H	O	Total
No Intervening Cause									
2a. Falls of roof	107	9	1	57	5	72	4	10	265
2b. Falls of side or face	190	32	3	8	—	24	6	8	270
2c. Flying splinters	58	5	—	25	5	17	4	3	117
2d. Dust	—	—	—	2	—	—	—	—	2
2e. Hand tools or appliances (other than haulage hand tools)	32	5	5	26	6	17	24	3	118
2f. Props, bars, chocks, or lids	69	21	7	48	3	13	2	2	165
2g. Packing material	—	—	—	18	—	4	1	1	24
2h. Lump of coal or mineral	12	—	1	2	—	1	2	1	19
2j. Girders, scaffolding, and pipes	7	3	—	3	1	17	2	—	33
3a. Power loader	—	—	—	—	—	—	1	—	1
3b. Boring machine	—	—	—	—	—	1	—	—	1
3c. Conveyor, face, or trunk	6	—	1	3	3	3	—	2	18
3d. Loader, gate-end, or main	—	—	—	—	—	—	1	1	2
3e. Material on or falling from conveyors or loaders	14	1	—	—	9	6	8	—	38
3g. Electric cable	—	—	—	—	—	1	—	2	3
3j. Cutter machine or cutter rope	2	9	—	—	1	—	1	—	13
4a. Tubs	1	—	—	1	5	8	92	3	110
4b. Haulage hand tools (clams, sprags, etc.)	1	—	—	—	—	—	3	—	4
4d. Cage or mechanical hoists	—	—	1	—	—	—	—	—	1
4e. Haulage rope or pulleys	1	2	—	—	—	2	7	1	13
5a. Fixed machinery	—	—	—	—	—	1	—	—	1
5b. Haulage track and retarders	—	—	—	2	—	2	1	—	5
6b. Animals	—	—	—	—	—	2	4	—	6
Insufficient detail reported (or no object)	33	1	4	12	4	16	9	4	83
Intervening Cause : Stumbling, Slipping or Colliding H1									
2a. Falls of roof	—	—	—	—	—	1	—	—	1
2c. Flying splinters	—	—	—	2	—	—	—	—	2
2e. Hand tools, etc.	5	1	—	—	—	—	—	—	6
3e. Material on or off conveyor, etc.	1	—	—	—	—	—	—	—	1
Insufficient detail reported	—	—	—	1	—	1	—	—	2
Intervening Cause : Action of Second Person H3									
2a. Falls of roof	—	—	—	1	—	—	—	—	1
2b. Falls of side or face	1	—	—	—	—	—	—	—	1
2c. Flying splinters	—	—	—	2	—	—	—	—	2
2e. Hand tools, etc.	1	—	—	—	—	—	—	—	1
2h. Lump of coal	6	1	—	—	—	—	2	1	10
3b. Boring machine	—	—	—	—	—	1	—	—	1
3c. Conveyor	—	—	1	—	—	—	—	—	1
3d. Loader	1	—	—	—	—	—	—	—	1
4a. Tubs	—	—	—	—	—	2	1	—	3
4e. Haulage rope or pulleys	—	—	—	—	2	1	—	—	3
5b. Haulage track	—	—	—	—	—	2	2	—	4
Insufficient detail reported	14	4	—	9	5	11	8	6	57

* C = colliers, M = machinemen, F = fitters, P = packers, L = oaders, R = rippers and repairers, H = haulage and pit-bottom staff, O = overmen, deputies, shotfirers, horsekeepers, stonedusters, underground electricians.

TABLE C

NATURE OF INJURY

Injury	C	M	F	P	L	R	H	O	Total
Lacerations	136	18	8	57	6	58	28	12	323
Bruises	167	31	6	65	19	80	54	11	433
Lodging of foreign body	57	6	—	29	5	18	6	1	122
Crushing	60	12	2	23	3	19	34	2	155
Sprains and strains	28	6	2	8	3	15	13	7	82
Fractures and dislocations	22	4	—	4	2	6	9	2	49
Burns	2	3	2	2	—	1	2	—	12
Traumatic amputations	2	—	—	1	—	1	1	—	5
Sepsis (no report of original injury)	6	—	—	1	1	1	2	—	11
Insufficient detail reported (or information not available at time of reporting)	82	14	3	32	10	27	36	13	217

* C = colliers, M = machinemen, F = flitters, P = packers, L = loaders, R = rippers and repairers, H = haulage and pit-bottom staff, O = overmen, deputies, shotfirers, horsekeepers, stonedusters, underground electricians.

TABLE D

SITE OF INJURY

	C	M	F	P	L	R	H	O	Total
Head	16	2	—	8	1	9	7	1	44
Face	8	1	—	6	—	2	1	2	20
Neck	3	—	—	—	—	2	1	—	6
Eyes	60	8	—	29	6	19	4	1	127
Back and spine	47	5	2	21	4	13	9	8	109
Chest	17	5	—	5	2	12	13	2	56
Abdomen	8	—	1	1	—	5	3	1	19
Hips and buttocks	1	—	—	—	—	—	4	—	5
Thigh	40	5	1	7	3	10	3	2	71
Knee	36	8	2	17	4	10	7	5	89
Calf	37	1	5	6	4	18	11	4	86
Ankle	15	3	—	9	2	8	10	3	50
Foot	50	9	—	13	8	32	24	4	140
Shoulder	15	6	—	6	1	13	4	1	46
Arm	15	5	1	6	1	8	7	2	45
Elbow	9	4	3	11	2	5	2	—	36
Wrist	7	2	—	5	—	5	6	2	27
Hand	61	8	2	15	3	12	19	4	124
Fingers	116	22	6	56	7	39	48	5	299
Insufficient detail reported	1	—	—	1	1	4	2	1	10

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THE TOXICITY OF NITROGEN PENTOXIDE

BY

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There is no evidence in the literature that nitrogen pentoxide (N_2O_5), the highest known oxide of nitrogen, has ever been the subject of a toxicological investigation. This gas rapidly breaks down to give nitrogen dioxide and oxygen, but is known to be stabilized by the presence of ozone, and several investigators (Schumacher and Sprenger, 1929; Johnston, 1951) have studied the complex system of equilibria which exists between ozone, oxygen, and the oxides of nitrogen. Gorodetskii (1936) has studied the gaseous products at silent and spark electrical discharges in air and has concluded that in the presence of excess ozone nitrogen pentoxide is the only oxide of nitrogen produced.

Our interest in the toxicity of nitrogen pentoxide was aroused by our preoccupation with the atmospheric contamination in a high-voltage insulator testing installation. The evolution of ozone in the vicinity of the brush discharge which attends this testing is evident by the characteristic odour, and it might be assumed that this gas constituted the chief toxic hazard were it not for the work of Thorp (1941, 1950), who has shown that ozone prepared from pure oxygen has a far lower toxicity than ozone prepared from air, and that the higher toxicity of the latter must be due to nitrogen oxides. Thorp, however, admitted that the toxicity of air containing ozone and nitrogen oxides (calculated as nitrogen dioxide) was greater than might be expected from the known toxicities of pure ozone and nitrogen dioxide.

In view of the observations of Gorodetskii (1936) and other workers it is an attractive hypothesis that the increase in ozone toxicity which accompanies the presence of nitrogen oxides is due to nitrogen pentoxide. The first step to establish this hypothesis is to study the toxicity of this substance. And this is the scope of the present investigation. The extent to which nitrogen pentoxide is responsible for the toxicity of ozone encountered in industrial atmospheres, and the steps which should be taken to control such atmospheres, will be the subject of a later communication.

The toxicity of the lower nitrogen oxides, notably of nitrogen dioxide, has been studied by many investigators on account of the occurrence of these gases in "nitrous fumes" encountered in certain industries. There has been, however, little systematic work on the toxicity of pure nitrogen dioxide to the rat, the species selected for the nitrogen pentoxide experiments, and as concentrations of nitrogen pentoxide in air in the absence of ozone cannot be prepared free from nitrogen dioxide, a study of the toxicity of this gas is also included in the present investigation.

Experimental Methods

Preparation of Nitrogen Dioxide Solutions.—Nitrogen dioxide was prepared by the controlled heating of dry lead nitrate (Addison and Thompson, 1949). The gas was dried over phosphorus pentoxide and condensed to a pale yellow solid in a weighed glass bulb cooled in a mixture of solid carbon dioxide and acetone. Too rapid heating of the lead nitrate resulted in the production of some nitrogen trioxide; batches contaminated in this way were evident by their greenish-blue colour and were rejected. The bulb was re-weighed and then connected to a tube dipping into chloroform and the temperature was allowed to rise. When the bulb was re-cooled, chloroform was drawn in and the bulb was weighed again. The solutions, which varied in strength between 1·0 and 1·5%, were not stable for more than a few hours and were prepared freshly each day.

For the subsequent colorimetric determination of nitrogen dioxide in air and in nitrogen pentoxide solutions, a standard curve was prepared by adding 0·1 ml. of a series of dilutions of the gas in chloroform to 50 ml. of the Patty and Petty (1943) modification of the Griess-Ilosvay reagent, in stoppered flasks. The colour was allowed to develop for 20 minutes with occasional shaking and the optical density was read at 520 mμ. By comparing the standard curve so obtained with a similar one from a series of sodium nitrite solutions, it

was shown that 54% of the nitrogen dioxide reacted as nitrite ; a figure somewhat closer to the theoretical 50% from the equation

$$2NO_2 + H_2O = HNO_3 + HNO_2$$

than is the figure of 57% obtained by Patty and Petty.

Preparation of Nitrogen Pentoxide Solutions.—Nitrogen pentoxide was prepared by the dehydration of fuming nitric acid with phosphorus pentoxide in the presence of ozone (Audrieth, 1950). The gas was absorbed in chloroform contained in a bubbler immersed in a carbon dioxide-acetone freezing mixture. The chloroform solution was analysed by adding 0·1 ml. of an appropriate dilution with chloroform to 5 ml. water and then determining the nitrate ion by the method of Barnes (1950), which involves the nitration of 2 : 4 xylenol. The solution was also analysed for nitrogen dioxide by the method described in the previous paragraph. The concentration of nitrogen pentoxide in the solution was found to vary between 13 and 23%, and that of nitrogen dioxide between 0·2 and 1%. The solutions were kept cooled with solid carbon dioxide and were stable for at least one week.

Preparation of the Test Atmospheres.—The apparatus for exposing experimental animals to test atmospheres of nitrogen dioxide and nitrogen pentoxide is shown diagrammatically in Fig. 1. The atmospheres were prepared by atomizing a solution of the gas in chloroform at a predetermined rate into a metered stream of air by means of the controlled fluid-feed atomizer described by Gage (1953). The solution was contained in the glass syringe A from which it was expelled at a known rate through the atomizer B into a stream of air from a compressed air line dried by the silica gel column C and metered by the rotameter D. The solution was atomized into the mixing chamber E, and the atmosphere was led through a glass tube into the exposure chamber F, which

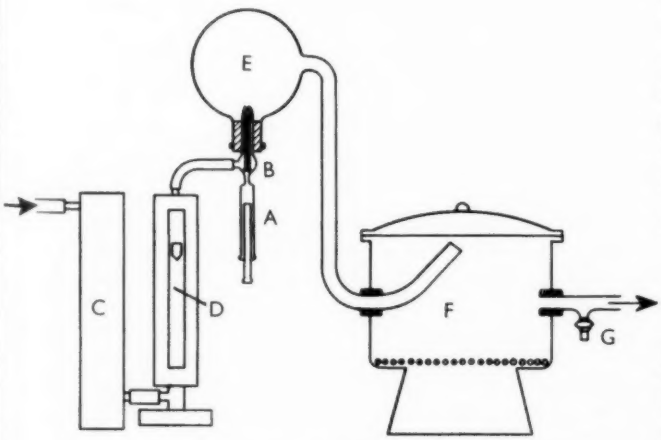

FIG. 1.—Diagram of apparatus for test atmospheres.

was constructed from a large glass desiccator bored with inlet and outlet holes and provided with a stainless steel wire mesh grid to support the animals. The exit tube carried a side-arm bearing a stopcock G through which the test atmosphere could be sampled.

In all the animal exposure experiments the air flow was fixed at 5 l./min. and the rate of feed of the chloroform solution at 0·00251 ml./min. ; variations in the test atmosphere were obtained by changing the strength of the chloroform solution. In all these test atmospheres the chloroform concentration was 150 p.p.m. v/v.

Analysis of the Test Atmospheres.—Analyses of the test nitrogen dioxide atmospheres leaving the exposure chamber were made by the method of Patty and Petty (1943). The results established that the predetermined nitrogen dioxide concentrations are maintained in the chamber whether animals are present or not.

Analyses of the nitrogen pentoxide atmospheres were made by drawing a known volume at 200 ml./min. through two bubblers each containing 1 ml. 1% 2 : 4 xylenol in glacial acetic acid and 9 ml. 85% w/w sulphuric acid. The tubes were heated at 35° C. for 30 min., and the contents were then diluted and analysed by the method of Barnes (1950). Nitrogen dioxide also nitrates this reagent to some extent, and experiments have shown that 27% reacts to give the nitro-derivative. An appropriate correction for the nitrogen dioxide present in the nitrogen pentoxide atmosphere was made after a direct determination of the former by the Patty and Petty method. By this procedure it was shown that about 85% of the predetermined nitrogen pentoxide concentration could be measured in the air leaving the empty chamber. When animals were present only about one-half of the expected nitrogen pentoxide was measured ; this diminution was attended by a slight increase in the nitrogen dioxide, but this was insufficient to account for the loss of nitrogen pentoxide. The concentrations of the test atmospheres quoted below for the animal experiments are those found by analysis and not the predetermined values.

Although there is no evidence in the literature that nitrogen pentoxide can oxidize chloroform, there is a possibility that a small amount of phosgene might be produced in this way. This contaminant was shown to be absent from an atmosphere containing 25 mg./m.^{3} nitrogen pentoxide by an appropriate test paper method (Department of Scientific and Industrial Research, 1939), under conditions where 1 p.p.m. v/v of phosgene would have been clearly detectable.

Nitrogen Dioxide Experiments

Single Exposures.—Male rats, mean weight 208 g., were exposed in groups of three to concentrations of 16, 40, 66, and 80 mg./m.^{3} NO_2 for four hours. At the lower two concentrations there were no toxic symptoms apart from restlessness ; at 66 and 80 mg./m.^{3} there was some salivation and restlessness and the animals showed slightly laboured breathing towards the end of the

exposure, but they soon recovered after removal from the atmosphere. Animals killed four and eight days after the exposure showed normal tracheae and lungs.

Similar experiments were made with older male rats ranging in weight from 300 to 400 g. The same symptoms were observed, but some of the animals at the highest concentration showed haemorrhagic patches on the lungs.

Repeated Exposures.—Fourteen male rats, mean weight 185 g., were exposed for four hours a day to 19 mg./m.^{3} NO_2 for 16 days. The animals showed no definite signs of discomfort and their breathing was normal. The increase in weight during the experiment was normal. A number of rats were killed at the end of the experiment and the lungs appeared normal.

The experiment was repeated with three rats at a concentration of 62·5 mg./m.^{3} for four hours a day for 20 days. The animals became restless and towards the end of each day's exposure developed laboured breathing; they recovered overnight and the effect on the respiration was not cumulative. The increase in weight during the period of the exposure was normal. Rats killed at the end of the experiment showed no abnormalities in the lungs.

Histological Examination.—Sections of the lungs of the rats killed after single and repeated exposures to nitrogen dioxide were prepared and stained with haematoxylin and eosin. All appeared normal except those from the large rats which had exhibited haemorrhagic patches on the surface of the lung; in these there was much congestion and extravasation of red cells into the alveoli, but no oedema was apparent.

Nitrogen Pentoxide Experiments

Single Exposures.—Groups of rats were exposed to a series of concentrations of nitrogen pentoxide for a period of four hours. The effect on the animals is shown in the Table.

TABLE
EFFECT ON RATS OF A SINGLE 4-HOUR EXPOSURE TO NITROGEN PENTOXIDE

Concentration (mg. m.^{3})		Rats			Deaths*	Symptoms
N_2O_5	NO_2	No.	Sex	Mean Weight		
5·3	2·8	4	♀	200 g.	None	Salivation and restlessness, later laboured breathing; rapid recovery after exposure
9·7	5·8	4	♀	230 g.	1 (24 hours) 1 (48 hours)	Dyspnoea after 1 hour
12·5	2·8	6	♀	220 g.	None	Dyspnoea after 1 hour, later frothy fluid at nostrils
13·7	2·3	2	♀	225 g.	1 (12 hours)	
20·4	3·5	4	♂	350 g.	2 (2–3 hours) 2 (12–16 hours)	Dyspnoea after 45 min.
21·3	10	4	♀	225 g.	1 (1 hour) 1 (16 hours)	Immediate dyspnoea, rapidly becoming severe; frothy fluid at nostrils

* Times in parentheses indicate delay of deaths after end of exposure.

The dyspnoea in these animals was characterized by a gasping inspiration, which in its severe form was attended by a violent contraction of the diaphragm and abdominal muscles.

The severity of the dyspnoea in the animals which survived the exposure decreased after their removal from the atmosphere, and their breathing returned to normal after a few days. All the animals which survived 12·5 mg./m.^{3} and more showed marked inertia for more than a week and during this period they failed to put on weight. In the animals which succumbed to the exposure death was in some cases preceded by violent convulsions; all the lungs appeared oedematous and emphysematous and there was a frothy, colourless fluid in the tracheae. All the survivors were killed one month after the end of the experiment and the lungs appeared normal.

Repeated Exposures.—Six male rats, mean weight 225 g., were subjected to 10 daily four-hour exposures of 2·5 mg./m.^{3} nitrogen pentoxide. From the fourth day onward breathing became somewhat laboured towards the end of each exposure period, with recovery overnight. The mean weight decreased slightly to 215 g. during this experiment. All the animals were killed at the end of the experiment, and the lungs appeared normal.

Six male rats were given 12 daily four-hour exposures of 4·25 mg./m.^{3}. During the first three days the animals were restless, and their breathing became laboured towards the end of each exposure period; later, as dyspnoea became more severe, the animals were prostrate. From the seventh day onward a clear fluid appeared at the nostrils. No animal died during the experiment but the mean weight fell from 190 to 150. Two rats were killed at the end of the exposure and the lungs appeared slightly swollen and emphysematous; in others killed a few days later the lungs appeared normal.

Histological Examination.—Lung sections (Fig. 2) from rats subjected to single exposures of 9·7 mg./m.^{3} or more of nitrogen pentoxide showed extensive oedema filling large areas of the alveolar space. There was widespread rupture of the alveolar walls, and these patches of emphysema were filled with oedematous fluid. No haemorrhage was apparent, and the alveolar capillaries were not congested. No trace of oedema could be found in the lung sections of rats exposed to repeated concentration of 2·5 mg./m.^{3}, but at the higher concentration there were small localized areas.

Discussion

The most notable symptom produced by exposing rats to concentrations of nitrogen pentoxide in air is acute pulmonary oedema, which becomes apparent after a single four-hour exposure to 9·7 mg./m.^{3} (about 2 p.p.m. v/v). Ten successive daily exposures to 2·5 mg./m.^{3} (about 0·5 p.p.m. v/v) gave evidence of lung irritation without oedema. It is evident that nitrogen pentoxide must be classed as a "lung irritant" gas, with a potency at least as great as that of phosgene and ketene.

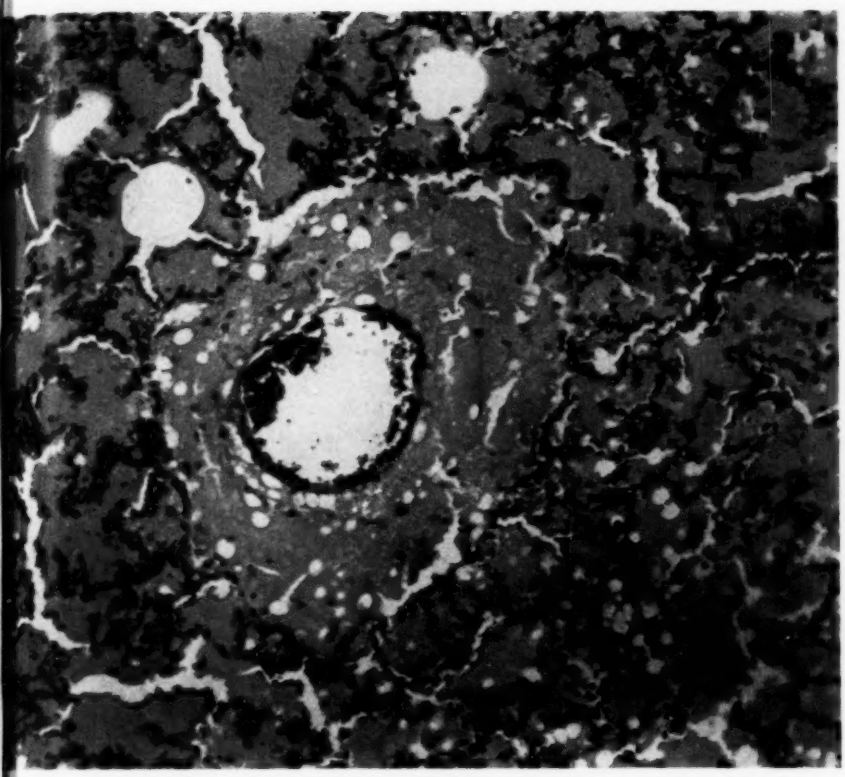

FIG. 2.—Section of rat lung after four-hour exposure to 9·7 mg./m.³ nitrogen pentoxide showing extensive oedema. × 130.

Nitrogen dioxide, which is the chief constituent of the " nitrous fumes " encountered in industry, appears as a lung irritant of a far lesser intensity. At the highest concentration used in these experiments, 80 mg./m.³, there was no sign of pulmonary oedema, though a few rats showed haemorrhage of the lung. This is in agreement with statements in the literature that 70 mg./m.³ is well tolerated (McCord, Harrold, and Meek, 1941). The small amount of nitrogen dioxide which unavoidably accompanied the nitrogen pentoxide in our experiments cannot be regarded as contributing significantly to the toxicity of the latter. Chloroform, at the concentration used in all these experiments, is without any detectable effect on the rat from the evidence of the exposures to the lower concentrations of nitrogen dioxide.

To what extent nitrogen pentoxide contributes to the toxicity of " nitrous fumes " is uncertain. It is probable that it is present in ozone produced by an electrical discharge in air, and its contribution to the toxicity of ozone will be discussed in a later communication. It is much less certain that it occurs to any significant extent in the " nitrous fumes " produced by other methods, and so far no method exists for the unequivocal determination of nitrogen pentoxide in a large excess of lower oxides of nitrogen.

Nitrogen pentoxide may be regarded as the anhydride of nitric acid, but its high toxicity cannot be attributed to the acidity produced when it comes into contact with the moisture of the alveolar walls. A similar hypothesis to account for the irritant action of phosgene has been countered by the observation that the amount of acid produced is far too small to have such an effect (Potts, Simon, and Gerard, 1949). There is no direct evidence in the literature that nitric acid vapour when inhaled has any specific irritant action on the lung, other than that derived from its acidity, and experiments in this laboratory have indicated that a single exposure to 63 mg./m.³ of nitric acid has no apparent effect on rats. These considerations lead to the conclusion that an appreciable part of the nitrogen pentoxide diffuses into the alveolar membrane and reacts as such with some component thereof before it reacts with water to form nitric acid. A similar mechanism for the action of phosgene and ketene has been suggested by Potts, Simon, and Gerard (1949).

The analytical method used for the determination of nitrogen pentoxide in air will not distinguish it from nitric acid. It has not, therefore, been possible to determine whether there has been in our experiments some conversion of nitrogen pentoxide to nitric acid by moisture in the atmosphere. If this were so, then the toxicity of nitrogen pentoxide would be even greater than that reported here, though in view of the conclusions which were reached concerning the fate of nitrogen pentoxide in the lungs, it seems improbable that this reaction takes place to any significant extent.

Summary

Methods are described for the preparation and analysis of test atmospheres of nitrogen dioxide and nitrogen pentoxide.

Inhalation experiments on rats have shown that nitrogen pentoxide is a lung-irritant gas with a potency of the same order as phosgene. Acute pulmonary oedema is produced by a four-hour exposure to 9·7 mg./m.^{3} (ca. 2 p.p.m.), or by 12 daily four-hour exposures to 4·25 mg./m.^{3} (ca. 1 p.p.m.). No oedema, but symptoms of respiratory distress were obtained with 10 daily four-hour exposures to 2·5 mg./m.^{3} (ca. 0·5 p.p.m.).

Nitrogen dioxide has a much lower lung irritant action ; 80 mg./m.^{3} produces no oedema but a few rats show haemorrhage of the lung at this concentration.

As nitric acid vapour is without obvious effect on rats at 63 mg./m.^{3}, it is concluded that the toxicity of nitrogen pentoxide does not derive from the nitric acid formed therefrom, but that nitrogen pentoxide reacts directly with some constituent of pulmonary tissue.

We wish to express our indebtedness to Dr. M. W. Goldblatt for his advice on the pathological interpretation of the animal experiments, and to Mr. J. S. Crozier for preparing the lung sections for histological examination.

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THE DEVELOPMENT OF LYMPH NODES AFTER INJECTION OF FLINT OF VARIABLE SIZE INTO THE LUNGS OF RATS

BY

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In experiments on rats by injection into the lungs of flint fractions of different sizes, ranging from under 0·5 to 8 microns (King, Mohanty, Harrison, and Nagelschmidt, 1953), it was observed that the hilar lymph nodes were enlarged after a certain time and that the different size classes of flint seemed to cause uneven development of these nodes. The effect was, therefore, studied in more detail and the findings are reported and discussed in the present paper.

Material

Lymph nodes were available from two series of experiments. In the first series 50 mg. of five different sizes of flint (<0·5, 0·5–1, 1–2, 2–4, 4–8 micron equivalent diameter) had been injected through an incision in the trachea into rats (30 for each size), and the animals that had not died otherwise had been killed at monthly intervals up to one year. This series (constant weight) had given some erratic results, probably on account of variable losses by regurgitation of dust immediately after injection (Table 2 in King and others, 1953), and the material was not quite complete, as some of it had been used for earlier recovery experiments and histological examinations.

In the second series, the same flint fractions had been injected perorally via the larynx in two or more weekly doses in different amounts so as to represent equal surface areas. Again each fraction was injected into 30 rats, which later were killed at various stages up to 500 days. This series (equal surface) had given more consistent results (Table 3 in King and others, 1953), suggesting a maximum fibrogenic action of particles between 1 and 4 micron diameter.

Technique

All lung and node material not used for blocks for sectioning had been kept in formol saline. The hilar lymph nodes were dissected if they could be found and freed as well as possible from adherent tissue. They were lightly wiped with filter paper and weighed separately for each rat. This gave the wet weights. After suitable bulking (the nodes from two or more rats from the same group being combined for analysis) the samples were dried to constant weight at 105° C., ashed at 450° C., the ash extracted with warm 2N HCl, and the residues obtained washed free from chloride, dried at 105° C., and weighed. These residues consisted of flint, and in control experiments it was established (*a*) that 95 to 98% of similar samples of flint could be recovered by this technique, and (*b*) that bulked flint recovered from nodes lost 99·4% by weight on treatment with hydrofluoric acid.

Results

Wet Weights.—The constant surface series, which had had fewer deaths and had given more consistent results, was analysed first. The node weights of single rats were somewhat erratic and a better picture is obtained by grouping the results, as shown in Table 1 and Fig. 1, for all wet weights from this series. It will be seen that the lymph nodes began to become enlarged after about four months or more. As the flint size increased the mature nodes, found after 10 months or more, increased in weight, with particles up to 1 to 2 micron in size, and thereafter they decreased again. The fraction 4–8 micron caused relatively little enlargement.

The wet weights of the nodes from the constant weight series are summarized in Table 2 and Fig. 2. There were many deaths and certain killing periods were omitted. For this reason the periods after injection which have been grouped are not quite comparable to those used for the constant surface series. Nevertheless the results are very similar except that swelling of the nodes began about one month earlier, namely, after three months. It can also be seen from a comparison of Tables 1 and 2 that 50 mg. of flint below 0·5 micron caused slightly larger nodes than did 8 mg. For the next three size classes the node weights were about the same in both

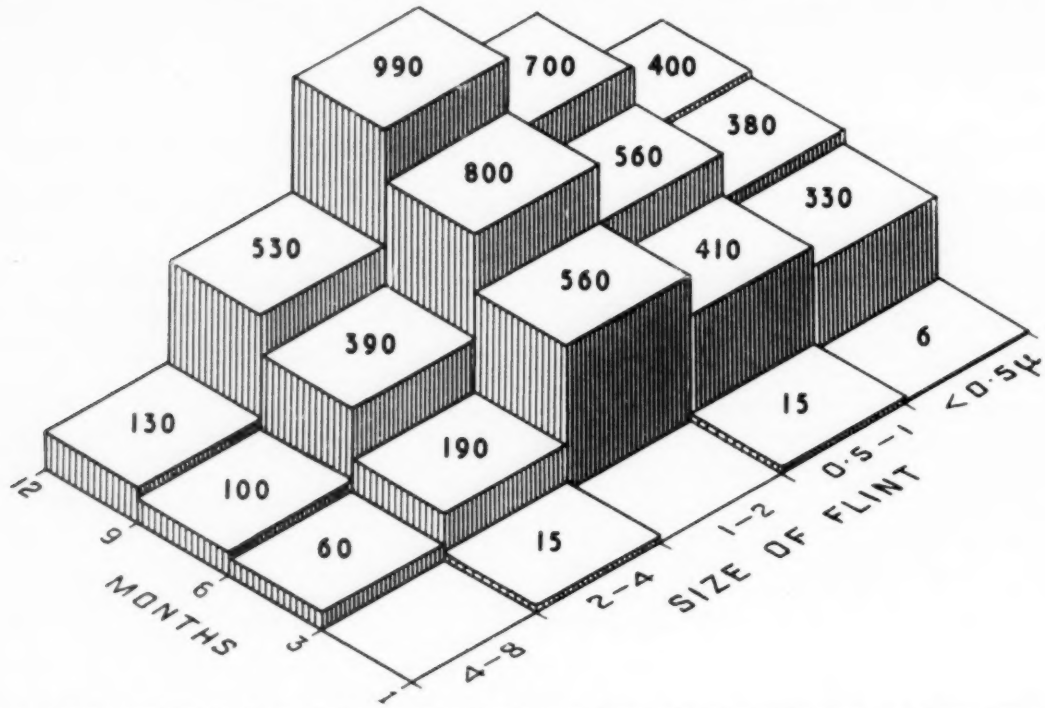

FIG. 1.—Graphic representation of the increase in weight of lymph nodes of rats which received flint particles of different size, and in different amounts, to give a constant surface area of 700 cm.², i.e., 199 mg. of 4–8 μ; 100 mg. of 2–4 μ; 42 mg. of 1–2 μ; 18 mg. of 0·5–1·0 μ and 8 mg. of <0·5 μ.

TABLE 1
MEAN WET WEIGHTS OF LYMPH NODES (MG. PER RAT) IN THE EQUAL SURFACE FLINT EXPERIMENT

Months	No. of Rats	Weight and Size of Flint Administered				
		8 mg. of <0·5 micron	17·5 mg. of 0·5–1 micron	42 mg. of 1–2 micron	100 mg. of 2–4 micron	200 mg. of 4–8 micron
1–3	3 or 4	6 ± 4*	15 ± 9	Nil	15 ± 4	Nil
4–6	6	330 ± 36	410 ± 55	560 ± 49	190 ± 67	60 ± 12
7–9	5 or 6	380 ± 53	560 ± 43	800 ± 98	390 ± 86	100 ± 27
Over 10	7 or 8	400 ± 37	700 ± 94	990 ± 102	530 ± 69	130 ± 46

* Standard error.

series and with the fraction 4–8 micron, 50 mg. gave larger nodes than 200 mg. This apparent anomaly is due to the presence of three sets of large nodes in three rats. If these are omitted the remainder of the node weights from 50 mg. of flint, 4–8 micron, averaged less than 150 mg. per rat. The nodes of normal rats increase with body weight and weigh approximately 10 mg. for a 200–300 g. rat and 50 mg. for a 400 g. rat. The average weight of the rats in these experiments was 150 g. at the time of injection, and rose to an average of about 250 g. at the times of the last killings, with a few of 300 g. final weight.

Recovery of Flint.—The concentration of flint and the total amount recoverable from the nodes of individual lungs were determined on a selected number of nodes and the results of 14 analyses are shown in Table 3. Although the flint values in general follow the trends shown by the wet weights there are certain noteworthy features. The flint as percentage wet (or dry) weight increases with the size of the flint, except for the fraction 4–8 micron, and for the larger fractions above 1 micron it increases with the duration of the experiment; in the nodes for the fractions below 1 micron on the other hand the flint as percentage wet weight is more or less constant.

Similar analyses were carried out on as many nodes as possible of the "equal weight" series, a number of nodes having been used previously in studies concerned with the total recovery of the flint from the animals. The results are given in Table 4 and it may be seen that not all analyses are based on the minimum of three rats, believed to be desirable for reliable results. This is due to the fact that a number of nodes had been used for earlier analyses concerned with total recovery from the animals, no wet weights being recorded at the

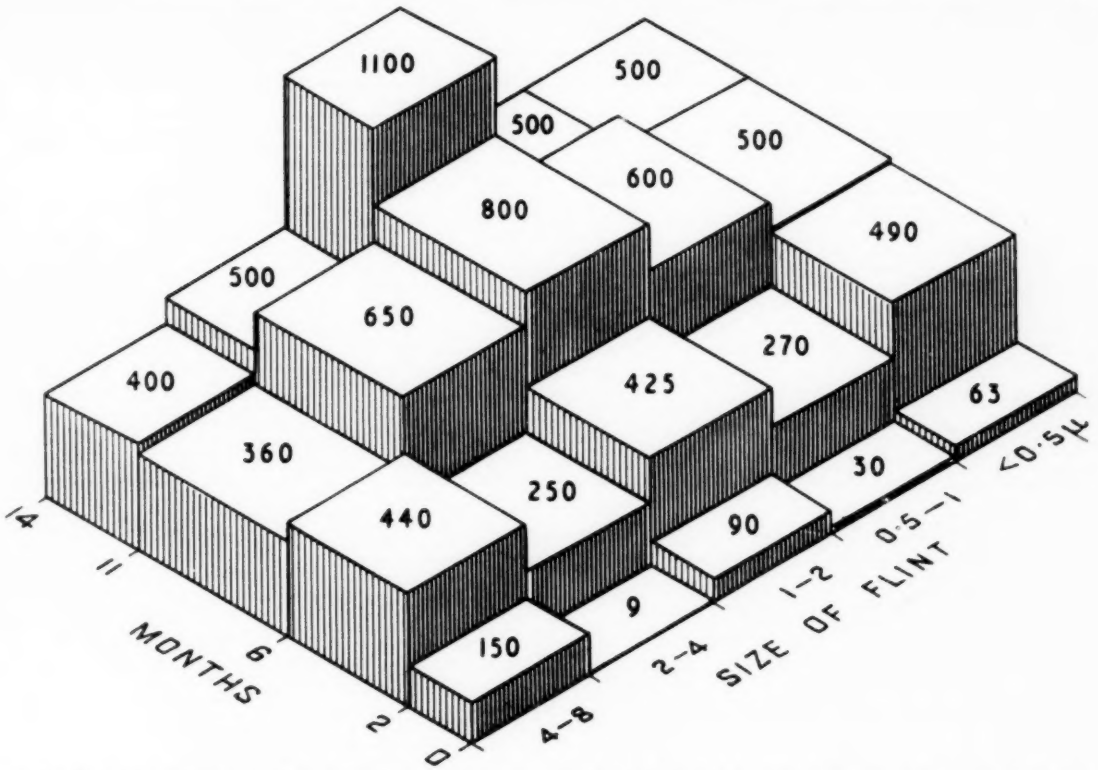

FIG. 2.—Graphic representation of the increase in weight of lymph nodes of rats which received 50 mg. each of flint particles of different size.

TABLE 2

MEAN WET WEIGHTS OF LYMPH NODES (MG. PER RAT) IN THE EQUAL WEIGHT EXPERIMENT (50 MG. FLINT INJECTED)

Months	Size of Flint in Microns				
	<0·5	0·5–1	1–2	2–4	4–8
0–2	(6)* 63 ± 32	(4) 30 ± 17	(4) 90 ± 35	(3) 9 ± 9	(5) 150 ± 62
3–6	(5) 490 ± 44	(9) 270 ± 50	(6) 425 ± 159	(3) 250 ± 128	(2) 440 ± 210
7–11	(5) 500 ± 96	(5) 600 ± 174	(6) 800 ± 161	(7) 650 ± 186	(6) 360 ± 165
12	(6) 500 ± 79	(2) 500 ± 20	(6) 1100 ± 186	(8) 500 ± 60	†(6) 400 ± 271

* Figures in brackets are numbers of rats in each group. † The mean of five nodes in this group is 130 but the sixth weighed 1,750 mg.

time. This accounts for certain gaps in Table 4. The trends shown by Table 4 are, however, very similar to those shown by Table 3. In particular Table 4 shows that even when equal weights were injected into the lungs more silica was found after 12 months with the intermediate size classes than with the finest fraction; this fraction <0·5 micron had given more silica in the nodes in the equal weight than in the equal surface experiment, which is reasonable as only 8 mg. per rat were given in the latter experiment. In most other cases the values of silica found in the nodes were similar for comparable size classes and durations, in spite of the widely different amounts given.

Tissue Sections

A representative selection of nodes from both series of experiments was sectioned and the degree of fibrosis and number of nodules were estimated from haematoxylin- and eosin-stained sections. The results are shown in Tables 5 and 6, to which the fibrosis found in the lungs has been added for comparison. Fibrosis of the nodes in general went only to grade 3. But one node in each series examined progressed to

TABLE 3

ANALYSES OF LYMPH NODES IN THE CONSTANT SURFACE (700 CM² PER RAT) EXPERIMENT*

Size of Flint (μ)	Weight Given (mg.)	Duration (months)	No. of Rats	Wet Weight (mg.)	Dry Weight (mg.)	Ash Weight (mg.)	SiO_2 (mg.)	Recovery (%)	Silica as percentage of		
									Wet Weight	Dry Weight	Ash Weight
<0·5	8	4–5	4	330	66·1	4·5	0·8	10	0·2	1·2	18
		8–9	4	320	67·3	4·6	0·9	12	0·3	1·4	21
		12	2	463	93·5	6·9	1·4	17·5	0·3	1·5	21
		17	3	513	108·5	6·7	1·4	17·5	0·3	1·3	21
0·5–1	17·5	4–5	4	405	78·6	5·7	1·9	10	0·5	2·4	33
		8–9	4	534	105·6	8·0	3·1	17·5	0·6	3·0	39
		12	2	681	139·0	10·0	3·2	18	0·5	2·3	32
1–2	42	4–5	4	578	108·5	8·7	3·2	8	0·6	3·0	37
		8–9	4	720	145·3	11·6	5·2	12	0·7	3·6	45
		12	2	940	187·4	16·95	8·2	20	0·9	4·4	49
2–4	100	4–5	4	197	41·2	3·2	1·2	1	0·6	2·9	37
		8–9	4	450	103·1	8·6	3·2	3	0·7	3·2	38
		12	2	631	134·8	14·5	7·5	7·5	1·2	5·6	52
4–8	199	4–5	4	49	—	—	Not analysed				
		9–13	5	156	26	2·2	0·5	0·3	0·33	2·0	24

* All results are mean values per rat.

TABLE 4

ANALYSES OF LYMPH NODES IN THE CONSTANT WEIGHT (50 MG. PER RAT) EXPERIMENTS*

Size of Flint (μ)	Duration (months)	No. of Rats	Wet Weight (mg.)	Dry Weight (mg.)	Ash Weight (mg.)	SiO_2 (mg.)	Recovery (%)	Silica as percentage of		
								Wet Weight	Dry Weight	Ash Weight
<0·5	3–5	5	464	101·5	6·1	0·9	1·9	0·2	0·9	15·5
	7–10	5	460	121·0	6·9	2·4	4·7	0·5	1·9	34·0
	12	5	—	141·8	8·9	2·9	5·7	—	2·0	32·2
0·5–1	3–5	9	243	53·6	4·0	1·1	2·2	0·4	2·0	26·7
	10	1	—	254·5	16·5	5·7	11·4	—	2·2	34·5
	12	1	—	96·0	8·4	2·7	5·4	—	2·8	32·1
1–2	5–7	3	735	168·7	11·4	4·5	9·1	0·6	2·7	39·8
	11–12	5	–	203·7	13·9	6·0	12·0	—	2·9	43·0
2–4	5	1	—	88·4	4·8	0·6	1·2	—	0·7	12·5
	7	1	—	230·3	12·0	2·4	4·8	—	1·0	20·2
	10	1	—	288·4	14·3	4·8	9·6	—	1·7	33·6
	12	6	—	122·0	7·9	3·4	6·7	0·7	2·8	42·7
4–8	0–10	6	—	94·5	3·9	0·2	0·4	—	0·2	5·1
	12	1	–	430·5	21·3	4·0	8·0	—	0·9	18·8

* All results are mean values per rat.

grade 5 fibrosis and these occurred in the mid-range of particle sizes, i.e., 0·5–1 micron in the constant weight series and 1–2 micron in the constant surface experiment. Thus, in terms of both severity and amount of fibrosis, the middle-sized particles produced more than the very small or the large ones.

Discussion

The removal of dust-laden phagocytes to the lymph nodes is one of the principal defence mechanisms against dust introduced into the lungs. It must be remembered that in these experiments all the dust was given in one or a few doses, and that therefore the findings do not necessarily represent what would be obtained in experiments using dusting cabinets. In animal dusting, dust accumulation in the lungs and lymph drainage are going on simultaneously, but in our technique the lung can be considered as a dust reservoir, and the lymph node enlargement is a function of amount, composition, and size of the material introduced. For this reason the study of the lymph nodes was believed to be of interest.

The results of the two experiments are similar, though in that with constant surfaces of flint the data are more complete and the results more regular. It is clear in both experiments that flint in the middle

TABLE 5

HISTOLOGY OF LYMPH NODES IN THE CONSTANT SURFACE AREA (700 CM.² PER RAT) FLINT EXPERIMENT

Size of Dust (μ)	Weight Given (mg.)	Period of Time (months)	Grade of Fibrosis	No. of "Nodules"	Fibrosis in Lung
<0·5	8	6	1	+	3
		10	2 Late	+ + +	4 Min.
		15	2 Late	+ + +	4
0·5–1·0	17·5	6	2	+ +	3
		10	2	+ + +	4 Max.
		15	3 Late	+	5
1·0–2·0	42·5	6	2	+ + +	5
		10	3	+ + +	5
		15	5	+ + +	5
2–4	100	6	1	+ +	4 Min.
		10	2	+ +	5
		15	3	+ + +	5
4–8	199	6	Few areas of fibrosis No definite nodules	—	2
		10	No definite nodules	—	2
		15	2	+ +	2

TABLE 6

HISTOLOGY OF LYMPH NODES IN THE CONSTANT WEIGHT (50 MG. PER RAT) FLINT EXPERIMENT

Size of Flint (μ)	Period of Time (months)	Grade of Fibrosis	Amount of Nodules	Fibrosis in Lung
<0·5	2	Occasional areas of fibrosis No definite nodules	—	—
0·5–1	7	2 Late	+ +	2 Late
	12	5	+ + +	3
1–2	8	3	+ + +	3
	12	3 Late	+ + +	1
2–4	8	2 Late	+ + +	2
	12	2 Late	+ + +	1
4–8	8	2	+ + +	1
	12	2	+	1

\+ Few nodules.
\+ + Moderate amount.
\+ + + Numerous.

Grade 1 = Loose reticulin fibrils with no collagen ; 2 = compact reticulin with or without a little collagen ; 3 = somewhat cellular but made up mostly of collagen ; 4 = wholly composed of collagen fibres and completely acellular ; 5 = acellular, collagenous, and confluent.

range of particle sizes produced the maximum effect, in lymph nodes as well as in lungs. The nodes were bigger, they contained more flint, and developed more fibrosis. This finding can perhaps be best explained by examining the results with flint of the smallest and the largest particle sizes. With flint of the smallest size (<0·5 micron) the nodes increased rapidly in size, but showed no further increase after six months. They contained less total flint and showed less fibrosis than those from rats receiving the middle-size ranges of particles. Although there was no increase in size after six months there was an increase in the quantity of flint present and an increase in the number of fibrous nodules and the maturity of the fibrosis. This implies that the early increase in weight was not all accounted for by fibrosis and was partly due to inflammatory or reactive overgrowth, which was later replaced by fibrosis of about equal bulk. The lesser degree of final fibrosis and enlargement was presumably due to the lesser total content of flint. The lower flint content is correlated with the dose given in the case of the constant area experiment, but not in that with constant weights of flint (compare Tables 3 and 4). Therefore it seems that either more of this very small flint was retained in the lungs or more was lost from the nodes. The former is unlikely since the lungs showed less fibrosis in these groups, and it seems possible that some of the flint was lost by passage through the nodes of a proportion of the very fine particles, and possibly also because of their greater solubility.

At the other end of the scale, flint of the largest size (4–8 micron) also reached the nodes only in small amount, and caused little enlargement and little fibrosis. The lesser degrees of fibrosis and enlargement are presumably the result of the smaller amount reaching the nodes ; and this may well be due simply to the mechanical difficulty of transporting particles of this large size.

In Tables 3 and 4, the flint found in nodes has been calculated as a percentage of the dose given under " percentage recovery," and it may be seen that with the smaller flint fractions the recovery in the nodes after one year reaches 18–20%. In other studies to be reported later, the recovery from lungs and nodes has been determined as a function of time, and total recovery from lung and nodes in these cases was of the order of 50%, so that the flint in the nodes forms an appreciable proportion of all the flint recovered.

Summary

Lymph nodes of rats from an experiment on injection into the lungs of flint of variable size were weighed and the amount of flint in the nodes was determined.

The nodes swelled more rapidly to their final size with the smaller than with the larger flint fractions. The fraction 1–2 micron gave the largest nodes and highest amounts of flint and the fraction 4–8 micron caused only little and erratic node enlargement. The effects of size of flint were very regular, as illustrated in Fig. 1. With the three finest size classes 18 to

20% of the dose given was recovered from the nodes after one year.

In attempts to interpret the finding it is suggested that the dust cells have difficulty in transporting the larger flint particles because of their size, that the smallest particles may be readily transported to the hilar lymph nodes, but are later partly passed on to other sites, and, possibly, partly dissolved, while those of medium size (e.g., 1–2 micron) are both readily transported and retained by the lymph nodes.

Mr. B. Hollands and Mrs. D. Attygalle gave valuable assistance with the isolation of the nodes and their histological assessment.

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THE EFFECT OF OILING THE COTTON ON THE AIRBORNE CONTAMINATION IN CARD ROOMS

BY

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A disabling chest disease characterized by bronchospasm (" byssinosis ") has, for many years, been recognized as affecting the workers in cotton blow rooms and card rooms (Collis, 1909), and has been attributed to inhalation of the airborne dust round the machines. It remains a serious industrial hazard in spite of measures which have been taken to reduce the dust, such as the improvement of ventilation in the mills and the use of vacuum instead of open stripping-brushes on the carding machines.

More recently, however, there has been coming into use a method of dust suppression by spraying an oil emulsion on to the cotton at an early stage of processing (Paton, 1948), and the Factory Inspection Department has reported an impression that the health of the card-room operatives has improved in those mills which have introduced " oiling " the cotton. We have therefore taken an opportunity of making quantitative measurements of the airborne material in the card rooms of a group of mills before and after oiling had been installed.

Any improvement in atmospheric cleanliness due to oiling the cotton must, of course, be considered in relation to its possible disadvantages. These may be classed under three headings: (1) difficulties of maintenance of the oiling equipment, (2) interference by the oil with the subsequent processing, and (3) interference with final yarn quality.

If the oiling equipment is properly designed and operated none of these factors should prove so serious as to prohibit the use of oiling, but a full discussion of this is outside the scope of the present paper.

The dust load in the air of a card room includes at least four distinguishable components: (1) short pieces of broken fibre, known collectively as " fly ", which is responsible for the major part of the visible cloud of dust; (2) fine dust particles from, say, 10μ down to submicroscopic sizes, probably derived mainly from the dried plant tissue debris or " trash " which passes through the machines with the cotton (Fig. 1); (3) bacteria, which are mainly soil and water organisms from the cotton fields and are present in extraordinarily large numbers in the card-room air; and (4) fungal spores and hyphae of which numbers are large, but in no way comparable with those of the bacteria.

FIG. 1.—Typical photomicrograph of card-room dust particles. × 1120.

The present paper deals with counts of viable bacteria, as collected in a Bourdillon-type slit-sampler on nutrient agar and incubated at 37° C. (Bourdillon, Lidwell, and Thomas, 1941); counts of fine dust particles in the range of 0·5 to 6μ in diameter, collected in a thermal precipitator and

counted under a 2 mm. oil-immersion lens (Green and Watson, 1935); and gravimetric estimations of the total airborne solids collected in small electrostatic precipitators (Drinker, 1932).

Results are reported for the conditions in the card rooms of a group of six cotton spinning mills before and after the introduction of oiling.

Experimental Plan

Each mill was visited three times: once immediately before oiling was begun, a second time as soon as the oiling equipment had been in operation long enough to ensure stable conditions for the tests, and finally in the following year as nearly as possible on the same dates as at the first visit. The final visit was timed thus in order to avoid a possible seasonal effect in the comparison with the initial visit, and the intermediate visit was included lest drastic changes such as complete alteration in the cotton mixings should take place before the final visit could be made. There were inevitably some changes in the proportions of the various types and grades of cotton in the mixings but, since each mill remained on the same class of work throughout, the same general quality of raw material was maintained as well as supplies allowed. Even the greatest change noted in the cotton used* was not obviously correlated with a corresponding change in the results observed for airborne contamination, for which the other variables in the experiment appeared to be of greater consequence.

Between the intermediate and final visits, however, there was, in general, a change in the crop year of the cottons which may well have affected their bacterial contents even though their commercial grades were unchanged. (This statement is difficult to establish with certainty, and is subject to many minor reservations, but the cottons were traced with the assistance of the Raw Cotton Commission back to their shipments and inferred crop years, so far as the records allow.)

The later visits to any one mill were made to include the same days of the week as the first visit so that any systematic variation throughout the week could, if necessary, be eliminated in the "oiling" comparison.

Since byssinotic subjects experience tightness of the chest and difficulty in breathing more severely on Mondays than on the other days of the week, visits on Mondays were included in the programme at as many mills as possible, in order to give an objective comparison between the mill atmosphere on Mondays and on other working days.

There were fluctuations in the conditions in the mills during the experiment, due to sporadic alterations in the operation of the ventilating systems, to the efficiency with which oiling was maintained, and to the numbers of carding machines in actual operation. These, however, arose from the day-to-day exigencies of production in the mills and were beyond our control. Where possible, steps were taken to avoid taking readings during a prolonged interruption of the normal conditions but, for the most part, such interruptions could be regarded as temporary and random, so that the means taken over the durations of the visits to each mill and over the whole group of mills give a good picture of the overall effect of oiling on the airborne contamination.

Counts of Bacteria and Dust Particles.—The resources available for these two measurements were insufficient to carry out general sampling throughout the room, and observations were therefore confined to a single site in each card room, the identical site being returned to on the later visits; this was chosen, in each case, to be as near as possible to the centre of the body of carding machines in production. Drifts of ventilating air may invalidate the implied assumption that a site thus chosen is representative of the whole card room, and variations in the counts from mill to mill may therefore be somewhat confused with variations from point to point in each card room. Nevertheless, the numerical results obtained do broadly reflect the subjective impressions of the amount of airborne contamination in each mill.

The visits made before the introduction of oiling had to be restricted to two days at each mill, in order to complete the tests throughout the group of mills in the limited time available before the oiling equipment was installed. Subsequent visits were extended to three days in every case.

Previous experience (Drummond and Hamlin, 1952) had shown that the bacterial counts in card-room air are very high and that the volumes of air sampled must be kept small to avoid overcrowding the Bourdillon sampler plates. Special alternative slits, narrower than the standard slit, were therefore provided for the sampler, and exposures were reduced to five or 10 seconds; the sampler turntable rotated once very five seconds. Under these conditions the contamination of plates during handling in the card-room air becomes of unusual importance and the result calculated from a single plate is subject to a large systematic error. By taking a number of plates in rapid succession using different

* This was at Mill D where the mixing was changed from 50% American and 50% Brazilian cotton at visit 2, to 100% American at visit 3. The figures in Table 1 show no sign of having been affected by this change.

volumes of aspirated air, and plotting the observed colony counts against air volumes, however, a straight line plot is obtained of which the slope gives the true count per unit volume, while the negative intercept on the volume axis represents the mean volume of contaminating air (Fig. 2). In the present work, sampler plates were taken in standardized groups of four

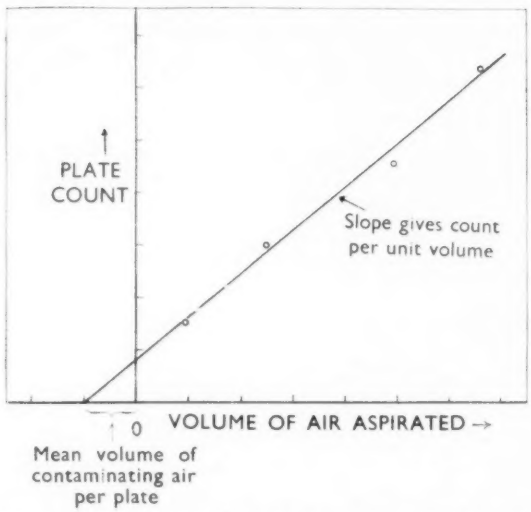

FIG. 2.—Derivation of bacterial count per unit volume from the observed counts in a group of Bourdillon sampler plates, when the contamination during handling in the sampled atmosphere is appreciable.
(The points plotted here are means; results for a single group of four plates show considerably more scatter.)

On the first, or pre-oiling, group of visits, 20 plates a day were taken in five groups, to give two figures for the morning and three for the afternoon on each day; on the subsequent, post-oiling, visits the plates were increased to 24 per day to give three figures for the morning and three for the afternoon.

The plates were taken with the normal work of the mill going on, though, where possible, exposures were avoided in the heavy dust clouds during stripping of the immediately adjacent cards. In the afternoon no observations of bacteria were made until the machines had been restarted for at least half an hour after the lunch hour break.

For the dust counts it was necessary, in general, to take runs of at least one hour to obtain satisfactory thermal precipitator traces, and this limited the tests to a single run in the morning and two runs in the afternoon on each day; there were a very few deviations from this routine, morning and afternoon readings always being obtained.

Runs were only taken when normal work was in progress, but they were not interrupted during the stripping of the adjacent cards since the heavy dust cloud persists for only a small fraction of the total time in a one-hour run.

Gravimetric Measurements of Total Airborne Solids.—Since dust deposits are much more quickly assessed by gravimetric methods than by counting, it was practicable to increase the number of days of the visit to each mill and to take six gravimetric samples simultaneously, in pairs, at three sites in each card room. Each precipitator head could, however, only be used for one run per day, since five or six hours were required to give a deposit which was weighable with sufficient accuracy.

The visits before the installation of the oiling equipment were restricted to two days at each mill, as before, but the later visits were extended to four and sometimes five days. The electrostatic precipitators were of the Drinker design (Drinker, 1932), with slight modification of the dimensions, and sampled at the rate of 1 cubic foot per minute. The deposit was collected on filter paper which was weighed before and after the sampling run, having been oven-dried before each weighing.

Results

From Table 1 it will be seen that, at the time of the first series of visits after the introduction of "oiling", the bacterial concentration had been reduced at five of six mills and that at four of these the reduction was statistically significant at the 5% level; at the sixth mill there was an unexplained, though significant, increase. The average reduction, over all six mills, was to 70% of the former count but, owing to the large scatter of the results, combined with the small number of mills visited, the figures do not establish the reduction as significant for the class of mills from which the sample of six was drawn.

The count of fine dust particles, on the other hand, was statistically significantly reduced (at the 5% level) at all six mills, the new average count being only 40% of the original. The improvement is better and more consistent than that found with bacteria, and the figures do establish a significant reduction for the whole population of mills.

The gravimetric measurements on the same visits showed some reduction in airborne material at every mill; this reached the 5% significance level at only three out of the six mills and the average reduction was to 79%, but nevertheless as a whole this indicates a significant effect for mills of this class. This is the figure for the present group of six mills for which parallel results on fine dust and bacteria are available. Over a wider range of mills

TABLE 1

RESULTS OF COUNTS OF BACTERIA, FINE DUST, AND AIRBORNE SOLIDS AT THREE VISITS

Mill	Visit* 1: Pre-oiling	Visit 2: 1st Post-oiling	Visit 3: 2nd Post-oiling	Visit 2 as % of Visit 1		Visit 3 as % of Visit 1		Visit 3 as % of Visit 2	
Bacteria (mean counts per cubic foot)									
A	10,000	6,900	16,500	68	−	165	+	241	+
B	2,900	2,200	7,200	76	O	248	+	326	+
C	14,500	3,600	6,400	25	−	44	−	180	+
D	9,400	5,800	6,000	61	−	64	−	105	O
E	5,200	7,400	8,500	142	+	163	+	114	O
F	6,100	3,600	5,600	60	−	92	O	155	+
Average standard errors of mill means	12%	11%	10%						
Crude overall mean percentages				70	O	129	O	180	O
Fine Dust (mean counts per c.cm. of particles between 0·5 and 6μ diameter)									
A	367	126	221	35	−	60	−	175	+
B	123	49	70	40	−	57	−	143	O
C	239	63	60	26	−	25	−	95	O
D	159	71	73	45	−	46	−	103	O
E	171	112	58	65	−	34	−	52	−
F	133	48	54	36	−	41	−	112	O
Average standard errors of mill means	8%	15%	13%						
Crude overall mean percentages				40	−	44	−	110	O
Total Airborne Solids (gravimetric load (mg. per cu. m.))									
A	5·69	5·37	6·11	94	O	107	O	114	+
B	2·34	2·16	4·20	92	O	179	+	194	+
C	3·96	2·39	3·03	60	−	77	O	127	+
D	4·97	3·54	3·87	71	−	78	O	110	O
E	4·47	2·74	3·89	61	−	87	O	143	+
F	2·27	2·20	2·71	97	O	119	O	123	O
Average standard errors of mill means	12%	7%	6%						
Crude overall mean percentages				79	−	108	O	135	+

− = percentage statistically significantly (at 5% level) less than 100%.
+ = percentage statistically significantly greater than 100%.
O = percentage not differing significantly from 100%.
* The numbers of observations available from each visit to each mill are rather more variable in the gravimetric investigation than in either of the counting investigations.

the gravimetric figures show a rather better average reduction of airborne matter.

In the final group of visits it was found that the improvement in fine dust counts had been maintained but that the gravimetric loads and, more especially, the bacterial counts, showed increases which were statistically significant at most of the mills. Insufficient care in the maintenance of the oiling equipment may be partly responsible for this deterioration at some of the mills, but the changed crop year of the raw cottons themselves could be the reason for a substantial part of the change in the bacterial counts.

Qualitative Changes in the Airborne Load after Oiling.—Since the gravimetric estimation gives a less favourable figure for dust suppression than does the count of fine dust particles, and the reduction in count of fine dust is maintained while the weight of total airborne solids increases under conditions of possibly less careful maintenance of the oiling equipment, it may be concluded that the fine dust is more easily and efficiently suppressed by oil than is the fly. This is as one might expect and is supported by earlier gravimetric observations at this Institute, in which "coarse fly" was distinguished from "fine fly plus dust". Our results, however, show no clear-cut change in the size-frequency distribution within the limited size-range of the optical counts, and we cannot confirm the reduction of median size in this range which the Factory Inspection Department has reported to be a consequence of oiling (Joint Advisory Committee of the Cotton Industry, 1952).

The analysis of the frequency distributions of types of bacteria before and after oiling has not been attempted.

Effects Other than that of "Oiling".—An analysis of variance shows that the differences from one mill to another are statistically highly significant and constitute by far the largest source of variation in the results in all cases. How much of this variation is due to differences between mills and how much to non-uniformity of the airborne load from point to point in a card room cannot, however, be determined from the available data.

It is also found that the concentrations generally vary significantly over the duration of a visit to a mill. The magnitude of this effect seems to be rather greater in the bacterial counts than in the dust counts.

A further possible variation which has been examined is that between Mondays and other days of the week. The results have been separately collected for Mondays and other working days for

TABLE 2
COMPARISON BETWEEN MONDAYS AND OTHER WORKING DAYS*

Visits	Bacteria (cu. ft.)			Fine Dust Particles (c.cm.)			Total Solids (mg./cu. m.)		
	Mondays	Other Days	No. of Mills	Mondays	Other Days	No. of Mills	Mondays	Other Days	No. of Mills
1 (Pre-oiling)	7,500	6,700	4	215	222	3	3·3	3·0	3
2 (1st Post-oiling)	3,900	5,000	4	78	75	4	3·3	3·6	6
3 (2nd Post-oiling)	9,900	9,100	3	121	96	4	3·5	3·6	5

*The figures are means for the groups of mills for which the results allow this comparison to be made. The number of mills in each such group is given in the third column.
None of the differences between Monday and other days, in this table, reaches statistical significance at the 5% level.

all cases where the figures permit of a comparison, and the means of these are given in Table 2. None of the differences between Mondays and other days is statistically significant and there is no clear tendency for either bacteria or fine dust particles or total airborne solids to be more concentrated on Mondays than at other times; this supports the general belief that the greater pulmonary discomfort felt by affected cotton workers on Mondays is due not to any special condition of the card-room atmosphere on Monday but to the subjects' different reaction to that atmosphere after the week-end break.

Summary

The airborne dust and bacteria in cotton card rooms have been measured in a group of mills before and after the introduction of equipment for oiling the cotton at the pre-carding stages.

The immediate effect of oiling was to reduce the counts of fine dust particles to 40%, and the counts of viable bacteria to 70% of their initial levels. The total weight of airborne solids estimated gravimetrically was reduced to 79% of the previous level.

Further measurements one year later, when a new crop of cotton was coming through the machines showed that, though the improvement in fine dust count had been maintained, the gravimetrically measured solids had increased again, and so, to an even greater extent, had the bacterial count. This deterioration is attributed partly to inadequate maintenance of the oiling equipment and partly to the changed crop-year of the cotton.

Analysis of the figures available showed no significant difference between the concentrations of airborne contaminants on Monday and on any other week-day.

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MISCELLANEA

A Simple Micromethod for the Determination of Lead in Small Amounts of Blood*

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In lead poisoning the determination of the concentration of lead in the blood is a useful aid in diagnosis and also in the supervision of treatment. For clinical purposes, an extremely accurate result is not necessary. It may be much more important to learn quickly that the lead content of the blood is within a certain significant range of values than to learn much later the value correct to 0·001 mg. per 100 g. of blood.

The advantages of the method to be described are: (1) The amount of blood required is only 0·5 ml., which can be obtained by finger prick. (2) No expensive apparatus is required. (3) All the manipulations are carried out in the one vessel. (4) A single determination can be done in two hours, or five in three hours with six flasks.

Briefly the method is to carry out wet oxidation of the organic matter in the blood, and then to determine the lead by the mixed-colour dithizone method.

Fischer (1929, 1934), and Fischer and Leopoldi (1934) have described very fully the properties of dithizone and of the compounds formed by it with a large number of metallic elements.

Many investigators have used dithizone for the determination of lead in biological and other materials, and the advantages of the mixed colour method for the determination of lead in various substances have been shown by Clifford and Wichmann (1936), Harrold, Meek, and Holden (1936), Hubbard (1937), Shiels (1938), and Bambach (1939, 1940). Nothing new is claimed in this method, except its application to determining lead in very small amounts of blood.

Spectrographic and polarographic methods for the determination of lead in a drop or so of blood have been described previously but the apparatus required is expensive, or not so suitable for the simultaneous determination of a number of samples. The present method requires a considerable amount of manipulative skill but no costly apparatus.

Principle of the Method

After the blood has been wet ashed to destroy organic matter and convert lead to the ordinary ionic form, the lead is determined by titration using the mixed-colour dithizone method. Enough dithizone solution is added to the test to produce a mauve solution, i.e., one containing approximately equal amounts of dithizone (green) and lead dithizone (red).

Exactly the same volume of dithizone solution is added to the blank and sufficient lead is then added to this until a match is made with the test solution. The amount of lead added should then be equivalent to the amount of lead originally present in the test. It is important that the titration be done with a mauve solution as the end-point, for with such a solution a more appreciable change is produced by one drop of lead standard than with a solution containing an excess of either dithizone or lead dithizone.

Apparatus

All glass apparatus is of "pyrex" glass. It must be cleaned thoroughly with nitric acid and rinsed well with distilled water before use. Water which has been double distilled in "pyrex quick-fit" apparatus or by an electric still has been found satisfactory.

Small Kjeldahl-like Flask.—This consists of an asymmetric bulb of volume 17 ml. with a long narrow neck (9 cm. long, 1 cm. wide) fitted with a ground-glass stopper (Fig. 1).

Micro-Kjeldahl Rack.—This holds flasks at an angle of about 45° and 1 in. above the flames of the microburners.

Graduated Pipette.—A 1 ml. graduated pipette has the tip drawn out to a very fine orifice and coated with paraffin which prevents the drops of lead standard solution from running back along the tip. Drops of volume 0·01 ml. can be delivered easily by this pipette.

Reagents

Lead Standard.—This is prepared from dry recrystallized lead nitrate. The standard solution is stored in paraffin-coated bottles and contains 1 mg. of lead per ml. The dilute standard solution used in the titration (0·005 mg. per ml.) is obtained by dilution of the stock solution and is freshly prepared each week.

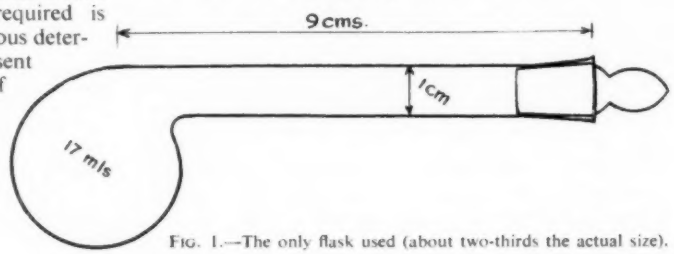

FIG. 1.—The only flask used (about two-thirds the actual size).

* Received for publication October 6, 1953

Dithizone Solutions.—Dilute solutions of dithizone in redistilled chloroform are freshly prepared each day. Two concentrations are suggested: Solution A, containing 0·5 mg. of dithizone per 100 ml. chloroform and solution B containing 0·25 mg. of dithizone per 100 ml. chloroform, but the concentration of dithizone solutions used are not critical as the same amount is always added to the test and to the blank. With experience, suitable concentrations of dithizone solution can be assessed by their appearance and it is then possible to prepare only the required amount (approximately 10 ml.) at a time.

Nitric Acid.—This is used redistilled in pyrex glass.

Nitrosyl-sulphuric Acid.—This is prepared by allowing redistilled nitric acid cooled in a freezing mixture to absorb sulphur dioxide which is passed into the acid for about three hours. This gives a solution of nitrosyl-sulphuric acid in sulphuric acid, which is used in order to obtain lead-free sulphuric acid by its decomposition.

Ammonium Citrate (30%).—A few drops of ammonia are added until the *p*H is approximately 9, and the solution is extracted with dilute dithizone until the chloroform layer is green. Excess dithizone is removed by shaking with redistilled chloroform.

Hydroxylamine Hydrochloride.—A saturated solution of reagent quality hydroxylamine hydrochloride is used.

Extractive Solution.—This is made up of 1% potassium cyanide and 1% ammonium citrate and purified from lead as is the ammonium citrate.

Ammonia.—Ammonia, 0·880, is heated and the evolved ammonia gas is collected in lead-free water, cooled in ice.

Method

Collection and Weighing of Blood.—The flask is cleaned thoroughly, drained and weighed. Sufficient blood is obtained by pricking a cleaned finger and allowing the drops of blood to fall down the neck of the flask (9 drops are approximately ½ g.). The flask and blood are then weighed. Any blood which remains on the side of the neck is washed down by acid refluxing during the digestion.

Digestion.—The flask containing the blood and another cleaned flask (the blank) are then treated in exactly the same way as follows:—

Nitrosyl-sulphuric acid, 1 ml., is added and the flasks heated gently for about five minutes. The flasks' contents are then boiled steadily until white fumes of sulphur trioxide fill the flasks and the contents of the test flask have charred. Nitric acid is then added dropwise to the fuming solutions until the contents of the test flask are a pale yellow. If the solution is kept fuming while the nitric acid is being added the digestion can be completed in approximately one hour. The solution is cooled, and approximately 2 ml. of water added and boiled to expel any nitrogen dioxide fumes. The resulting solution is cooled. The final solution should be a very pale yellow.

Exactly the same amounts of the reagents are added to the blank as to the unknown.

Determination of Lead by Mixed-colour Dithizone Method.—The stoppers are placed in the flasks and the reagents, 1 ml. ammonium citrate and 1 ml. hydroxylamine hydrochloride, are added to both flasks, which are shaken after each addition. Sufficient ammonia is used to make *p*H 9·0. (Test with *p*H papers by inverting the flasks to wet the stopper, removing the stopper after reinverting, and placing it on the *p*H paper.) Then 1 ml. extractive solution and 1 ml. dithizone solution B are added.

The flasks are then thoroughly shaken and after checking the *p*H, which should be the same in both the blank and the test, they are inverted so that the chloroform-dithizone layers can be compared. If the colour of this layer in the test ranges from blue to pinkish mauve no adjustment is necessary. However, if a pink is obtained, dithizone solution is added ½ ml. at a time until sufficient excess of dithizone is present to produce a mauve, the same amount being always added to the blank. For the first ½ ml. the dithizone concentration used is 0·25 mg. per 100 ml., but after this addition the most suitable concentration is 0·5 mg. per 100 ml. From the number of millilitres of dithizone solution required to obtain a mauve-coloured chloroform-dithizone layer in the test the approximate titration value can be gauged.

Vol. Dithizone Solution	Vol. of Lead Standard Producing Mauve (ml.)	Vol. of Lead Standard Producing Pinkish Mauve (ml.)
1 ml. solution A	0·075	0·10
1½ ml. solution A	0·125	0·15
1½ ml. solution A + ½ ml. solution B	0·20	0·25
1½ ml. solution A + 1 ml. solution B	0·30	0·35
1½ ml. solution A + 1½ ml. solution B	0·40	0·45

By adding dithizone solution in this way a suitable colour for comparison can be obtained for values of lead up to 0·45 ml. Lead standard (corresponding to a blood lead value of 0·00225 mg. per ½ g. of blood) and the maximum volume of dithizone solution used is 3 ml. For blood lead values greater than 0·45 mg. per 100 g. (indicated by the formation of a red with very little shaking, after the addition of 2½ ml. dithizone solution) a stronger concentration than ½ mg./100 ml. can be used for the last addition of ½ ml.

When the colour of the chloroform-dithizone layer has been adjusted to a mauve, and the same amount of dithizone has been added to the blank, the titration is carried out.

Dilute lead solution is added to the blank from the graduated pipette and after each addition the flask is shaken thoroughly, inverted, and compared with the chloroform-dithizone layer in the test flask. When the colours of these layers match, the amount of lead added from the pipette equals the amount of lead in the weight of blood taken. When the end-point is near the lead solution is added one drop (0·01 ml.) at a time. The final titration value is obtained in the following way: It may be found that addition of 0·10 ml. of lead solution

produces a colour in the chloroform-dithizone layer which is slightly bluer than the colour of this layer in the test and that a further addition of 0·01 ml. produces a colour which is slightly pinker than the test. Hence, the titration value is between 0·10 and 0·11. It is then possible to judge between these two values depending on whether the colour of the test is nearer the colour produced in the blank by 0·10 or 0·11 ml. of standard solution, e.g., if it is exactly midway between the two, the titration value is taken as 0·105.

If the amount of lead solution added to the blank at any time during the titration gives too great a colour change, then back titration can be carried out, that is, more lead can be added to the test until the colours match.

Precautions

Care must be taken to digest the sample completely. The colour of the aqueous layer during the final titration should be pale yellow.

The amount of dithizone used should be adjusted so that the colour being compared is mauve. If too much dithizone is present the pink of the lead-dithizone is obscured and the titration is not sensitive. If too little dithizone is present the colour is too pink and again a suitable match cannot be obtained. Possibly, the final colour to aim for may vary somewhat with different observers, but usually the mauve seems to be the most sensitive.

Results

The method was checked as follows :—

Known amounts of lead were added to normal blood by another analyst and the normal blood lead value was subtracted from the value obtained by titration of the reagent blank. It was, therefore, necessary to do a blood blank at the same time as each series of tests.

The results are summarized in the Table.

Discussion

It should be emphasized that in contrast to the procedure in other methods, in this method the whole of the procedure, including collection and weighing of blood, the wet oxidation, the addition of reagents, the extraction of lead dithizone into the chloroform layer and the final matching are all done in the same vessel. This keeps the volume of reagents down to a minimum and avoids manipulative errors due to the use of separating funnels, transfer of solutions from one vessel to another, and washing out of vessels to secure last traces of transferred solution, filtering, and so on. When dealing with small amounts of lead these points are very important.

Bismuth or thallium, if present, would interfere. However, in the absence of bismuth medication the occurrence of this element in the blood is extremely rare. The presence of thallium is so rare that in ordinary practice it can be ignored.

TABLE
SUMMARY OF RESULTS

Amount of Lead Added (mg./100 g. blood)	No. of Determinations	Recovery (%) with Standard Errors of Means
0·00–0·09	10	111·6 ± 9·95
0·10–0·19	10	98·5 ± 3·37
0·20 and over	5	97·95 ± 2·03
All values	25	103·6 ± 3·10
Values 0·10 and over	15	98·6 ± 2·4

Summary

A simple and inexpensive method for the determination of lead in small quantities of blood which can be obtained by a finger prick is described.

Five determinations can be done in three hours.

Results are quite accurate enough for clinical purposes, the average percentage recovery for all values (15) equal to or greater than 0·10 mg./100 g. of blood being 98·64 ± 2·4 and the average percentage recovery for all values (25) 103·63 ± 3·10.

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Three Approaches to the Study of Personality*

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Human personality has since time immemorial provided an attractive subject for philosophers and writers, but only very recently has it come within the purview of students committed to use scientific methods of enquiry. Not unexpectedly, these pioneers found their material less amenable to controlled investigation than had been the case with that studied by physicists and chemists, anatomists and physiologists. Two other difficulties soon became evident, however. Of these, one was the simple fact that the relationship between the student and the object of study was of so unique a kind as to demand some totally new departures in method ; the other, the consequences for generalization implied by almost limitless variations among the individual units concerned. To such formidable obstacles there were many possible patterns of response ; many readers will have made up their minds long ago to stick to Shakespeare and they are not advised to attempt the digestion of any of these three books. Their appeal can only be to those who still believe strongly that human personality should be, at least to some extent, susceptible of objective description, classification and assessment, and that in spite of inherent limitations, human behaviour should be partially predictable.

Of the three volumes, that by the late Bernard Notcutt, Professor of Psychology in the University of Natal, is without doubt the easiest to read. He described his book as " an attempt to choose, from among the great variety of current psychological concepts and methods, those that have the best promise for the future ", and its purpose as " more to evaluate than to describe the activities of psychologists ". His choice and his evaluations were evidently and understandably affected by his own preference for a combination of what have been called the holistic and longitudinal approaches to the study of personality. Dr. Eysenck, Reader in Psychology at the Institute of Psychiatry, University of London, did not set out to choose and to evaluate, but in his latest book continues to affirm with characteristic vigour his adherence to the atomistic and cross-sectional approaches. This is not, however, solely or perhaps even mainly a matter of preference, for he adduces evidence to show that, for prediction purposes at least, these non-global methods are so far superior.

The time has certainly come when it is no longer possible to assume that every educated reader or listener will interpret the term " scientific " in the same way. For this reason it is essential to say what it meant to Notcutt and Eysenck as students of the psychology of personality. The former (p. 3) stresses three aspects of the scientific method as particularly important for this purpose. There are (1) the formulation of exact, testable hypotheses ; (2) the need for publicly available methods and results which can be repeated by any competent observer ; and (3) freedom from moral and aesthetic qualms about what is worth studying and reporting. He lists as secondary *desiderata* such features as quantification, controlled experimentation, and the development of systematic classification and general principles. Eysenck (flysheet) quotes J. S. Mill as his mentor for an attempt to draw a measure of agreement out of a large number of studies by many investigators, and for claiming that, because factor analysis is the means by which such agreement is possible, it should be adapted for use with the topics where little or no agreement can be found. He therefore places his emphases on all of those features (primary and secondary) listed by Notcutt, but clearly regards them as but means to a single end, that of classification and the statement of general principles. Notcutt is interested mainly in persons as going concerns, and is only secondarily interested in the advancement of a science of persons : Eysenck is primarily a scientist, and studies personality as a natural phenomenon. Both recognize (Notcutt explicitly, pp. 13–14) the divergence of aim and its parallel in medicine in the differing emphasis of clinician and scientist. For reasons themselves largely psychological it is difficult today to find a " clinical scientist " in either medicine or psychology, and but little easier to achieve a genuine mutual respect as a working basis.

This personal difference is well reflected in the general approach of the two authors. Notcutt is warmer, more " humane ", and tempted to generalize without providing adequate evidence ; Eysenck rather more detached, decidedly impersonal, and abounding with facts and figures. A few samples will suffice to bring this out. On p. 165 Notcutt says flatly, and without supporting evidence, " a self-rating scale is not even the roughest approximation to a true picture of the person ". By contrast, Eysenck devotes two pages, at the end of a 30-page chapter on questionnaires and inventories (which bristles with factual data and references), to a balanced consideration of their inherent weaknesses under various conditions. Similarly, Notcutt is so untroubled by the restrictions of scientific method that on p. 171 he is able to state unabashedly that " the most fruitful use of projective analysis is the *interpretation* of attitudes " (reviewer's italics). However true this may be for the clinician seeking " leads " in dealing with the single case, it is just the sort of subjective feature which causes psychology to present so contradictory a picture of personality. This is not the same as saying that there are no contradictory elements in personality ; to the scientist, the challenge is to accommodate the contradictions in a lawful manner. Characteristically, Eysenck's approach to the type of test incorrectly called " projective ", exemplified by the Rorschach and by the

* *The Psychology of Personality*. By Bernard Notcutt. (Pp. 259. 21s.) London : Methuen & Co. Ltd. 1953.

The Structure of Human Personality. By H. J. Eysenck. (Pp. xiii + 344. 37s. 6d.) London : Methuen & Co. Ltd. 1953.

Personality Tests and Assessments. By Philip E. Vernon. (Pp. xi + 206 ; illustrated. 18s.) London : Methuen & Co. Ltd. 1953.

Thematic Apperception Test, is to quote the results obtained by methods which avoid the very interpretation which Notcutt values so highly, and to integrate the findings with those obtained by other methods.

This is perhaps the appropriate point at which to mention the third volume in this Methuen trilogy which Professor C. A. Mace has edited. It is by Professor P. E. Vernon, of the Institute of Education, University of London, and is best described as a brilliantly annotated guide to the present possibilities of personality assessment. Those readers who are familiar with the pink-covered reports of the Industrial Health Research Board (alas, discontinued since 1947) may have read Vernon's 1938 report on "The Assessment of Psychological Qualities by Verbal Methods", to which the present volume is in some ways a successor. He assumes from the start (p. 4) that readers will know how to evaluate a validity or reliability expressed as a correlation coefficient, or that they are prepared to find out. To the present writer, this seems less unreasonable than might appear; if a non-specialist wants to use the work of the specialist, then there are minimum requirements to be met. So far as psychological tests are concerned, it means correlation coefficients, variance estimates, and levels of significance. Readers will be grateful for his definition: "A psychological test, by presenting a standardized task or situation, elicits a sample of the testee's behaviour which can be objectively scored and compared with norms of performance, and which has been proved to be predictive of future occupational or other behaviour" (p. 31), and for the frankness of his next sentence: "In the field of personality this is an ideal rather than an actuality". Here Eysenck is inclined to be a little more confident, for he quotes data to support a claim that the main "dimensions" can be measured with validities but little lower than those regarded as satisfactory for intelligence tests. However, the results are not unequivocal, and obtained from rather atypical groups such as hospital patients and staff and soldiers. In the industrial experience of the writer, such objectively scored tests of personality have proved useful.

Professor Vernon has a good deal to say about the use of the interview for assessing personality which could with profit be read by medical men, both in and out of industry. While recognizing its usefulness (when designed very carefully for a specific purpose) as one of a number of approaches, he makes it clear (as does Eysenck in a chapter on ratings) that its principal characteristics are unreliability and doubtful validity. This he attributes to the scope it gives the interviewer "to jump to false conclusions, and to be influenced by prejudices and unsound theories". In this connexion he quotes (p. 28) from an important American study in which it was found that the degree of confidence felt by the judges in any method (involving personal contact, but excluding objective tests) provided completely misleading indications of its true value! This may not be irrelevant when attempting to evaluate Notcutt's enthusiasm (pp. 157, 188 et seq.) for the "achievements" of the War Office Selection Boards and the equivalent American procedures. The objective evaluations of validity for these methods are more sober, and it is likely that Notcutt's judgement was too much affected by his dislike of tests as atomistic, in contrast with the holism of the Gestalt school to which he adhered. Vernon is more balanced in his view than either Notcutt or Eysenck on this issue.

Quite apart from the merits and demerits of the books themselves, in what way does their appearance add to our knowledge of human personality? Is the confidence of the intelligent, educated and enquiring non-psychologist likely to be enhanced or shaken as he considers our achievements to date? And are the prospects good for fresh advance? To these questions some answer must be essayed, but before doing so one point must be made clear if writer and reader are not to be at cross-purposes. The point in question can be simply stated: the answers to these questions will depend for their meaning and value upon whether or not they imply a belief in the desirability and feasibility of studying personality by rigorous scientific means. If the reader does not accept that implication, then it is likely if not indeed certain that he will reject the answers and not trouble to read any of the books. If he does not accept it, but shares the "holistic and longitudinal" views of Notcutt, he will probably ignore the given answers but read the three books in the order Notcutt, Vernon, Eysenck; the chances of his finishing the last are probably slim! From this incomplete coverage of the possible responses it will be evident that the writer himself accepts the implication, and his answers should be evaluated accordingly. To the first question, In what way does the appearance of these three books add to our knowledge of human personality? the answer is affirmative. Eysenck and Vernon bring together in manageable compass a previously ill-assorted and apparently incoherent mass of data, showing in the process that some intelligible pattern is emerging. Notcutt, approaching from almost the opposite direction by different means of transport, hastens to clothe the framework which they have so indecently exposed, lamenting the while that it is inhuman and lifeless. To the second question, How is the confidence of the layman likely to be affected? the answer is probably "Not at all", because facts do not carry much weight where self-acknowledged experts are involved; but to this there can be exceptions if the non-psychologists are truly enquiring and very persevering. Finally, are the prospects good for fresh advance? They are in some ways better than they were, but we are desperately short of first-class minds, committed to the rigorous demands of the scientific method while capable of formulating new hypotheses which are testable. The psychoanalytic and the Gestalt schools were rich in hypotheses and weak in scientific method, the factor-analysts and test-oriented investigators are on surer methodological foundations, freer from temptation to generalize, but in danger of sterility.

BOOK REVIEWS

Medicina del Lavoro (Industrial Medicine). By F. Molfino. (Pp. 600 ; 91 figures. Lira 7,000.-) Turin : Edizione Minerva Medica, S.A. 1953.

The principal author of this book is Professor Francesco Molfino of the Institute of Industrial Medicine of Genoa. The book is printed on art paper throughout in a large and clear type and the illustrations are of high quality and clearly reproduced. There is a good subject index. The quality of production is excellent ; not only does it do justice to the country which produced Ramazzini, but British readers may well marvel at the production of such a treatise from a town which they know mainly as a seaport.

A clinical approach is used throughout. Each industrial disease is considered in turn under the following headings : historical notes, aetiology, pathogenesis, pathological anatomy, symptomatology, diagnosis, prognosis, treatment, prevention, and legislation. The diseases themselves are arranged in groups, beginning with dust diseases of the lung. Then follow diseases due to physical agents, infective and parasitic diseases, diseases due to toxic agents, allergic conditions, occupational tumours, skin diseases, and diseases associated with fatigue and stress. The emphasis throughout is on clinical, physiological, and pathological aspects of the occupational maladies considered. Only brief accounts of prevention and legislation are usually given and there is generally no description of the industrial processes themselves. Little indication is given of the incidence of the various diseases in Italy. A list of references, included after each disease, is often a long one, and altogether there are about 1,200 references, but references in the English language are not numerous. The chief value of this book to the English reader will be in the references under each disease, which are mainly in Italian, French, and German. It is, however, a little disconcerting to find many names quoted in the text which are not mentioned in the list of references.

Unfortunately the opening section on silicosis is somewhat sketchy, but it would provide a reasonably well balanced account for a practitioner who wanted a brief general review of the subject. There is a series of 10 radiographs, clearly reproduced, most of them of advanced stages ; the term " reticulation " (whose abandonment was recommended at the I.L.O. conference on pneumoconiosis in 1950) is little used and early stages are not well illustrated. There is no mention of standard films. Curiously, the clinical signs of the supervention of tuberculosis are omitted. A recommended safe maximum of 200 silica particles per c.c. is given, but there is no description of dust-counting techniques.

Asbestosis is similarly briefly described, with three good radiographs and four photomicrographs ; incidence and prevention are scarcely mentioned. The occurrence of carcinoma of the lung as a complication is mentioned but no evidence is quoted.

Byssinosis and bagassosis are briefly described. There is no mention of fungus infections of the lung (" farmer's lung ") but " baritinosis "—a benign pneumoconiosis of baryta workers—will be new to most English readers.

In the section on diseases due to physical agents there is a long discussion of the physiological processes and symptomatology of heat stroke, no doubt appropriate in a hot country.

The section on caisson disease is magnificent and should be read by all interested. There are excellent photographs of the working processes, a good account of the selection of employees, and a full physiological description with calculations of the distribution of gases in the blood according to Henry's Law and calculation of decompression times. Ten radiographs are given showing osteo-arthritis, mainly of hip, shoulder, and knee, developing in caisson workers ; small rounded areas of rarefaction near the epiphyseal line with patches of sclerotic thickening are considered to be characteristic and to differentiate this form of osteo-arthritis from others. The diver is not forgotten and a good account is given of physiological aspects of diving to different depths and of the hazards involved. Some aspects of aviation medicine are briefly described.

The polymorphism of the electrocution syndrome is adequately described. In first-aid treatment, Schaeffer's method of artificial respiration is recommended because of the necessity of avoiding inhalation of vomited matter ; there is no mention of the Holger-Nielsen method. Lumbar puncture is recommended when there is a rise in cerebrospinal fluid pressure, but no mention is made of the risk of producing a medullary pressure cone.

The account of nuclear physics and the production of different types of radiation is incomplete and too brief. No account of the blood changes caused by radiation is given, nor is there mention of the wearing of a standard dental film by those exposed to risk.

The short section on ocular diseases caused by radiant energy is by Professor Maione, assistant in the ophthalmic clinic of the University. The account is clinical and there is no description of working processes. Different types of goggles are mentioned but there does not appear to be a standard glass for different purposes, comparable to the British Standard specifications for welders' glasses.

Under diseases caused by vibrating tools a description

is given of Raynaud's phenomenon, which is said to occur more frequently in the left hand, and occasionally to progress to trophic changes ; the statement that the condition commonly occurs at the end of the day's work does not accord with published experience in this country. Disabling angioneurotic phenomena apparently qualify the sufferer for industrial disease benefit. Osteoarthritic manifestations in the elbow and wrist are briefly described.

The section on occupational deafness is by Dr. R. Castello, assistant in the Otorhino-laryngology Clinic of Genoa University. A good account is given of the aetiology and pathogenesis of the condition. The author does not believe that there is any difference between the types of deafness found in different noisy occupations, all having the same characteristic high-tone deafness (" C5 dip "). This is regarded as being generally sufficiently characteristic to differentiate it from presbyacusis. Prevention rests, in order of importance, on engineering measures to reduce noise production, the selection of employees who have no previous otopathology, periodic audiometry of exposed workers, and finally the provision of ear defenders. There is no mention of ultrasonic vibrations. Occupational deafness qualifies the sufferer for benefit payments in Italy in boiler-making and certain other specified occupations.

The section on infective and parasitic diseases contains clinical descriptions of foot and mouth disease, anthrax, Q fever, swine fever (erysipeloid of Rosenbach), swineherd's disease (due to Leptospira pomona), glanders, and ankylostomiasis. At first sight this appears to be a rather strange collection, but it must be admitted that most of these are of occupational origin. Of rare occurrence in this country, they are no doubt more common in Italy ; figures of incidence are, however, given only in respect of anthrax (823 cases of malignant pustule were notified in 1942), and Q fever of which 800 cases were recorded up to July, 1951. Ankylostomiasis appears now to be occurring in agricultural workers, but no figures of incidence are given.

The section on toxicology, of 260 pages, contains good and fairly detailed descriptions of the metallic and other inorganic toxic substances. The effects of organic phosphorus compounds are clearly described. Lead poisoning is described in detail, with rather surprising reliance in diagnosis on the *x*-ray appearances of a barium enema ; four radiographs are reproduced, showing " saturnine colitis ", and there is a full description of " saturnine gout " which, however, does not appear to differ essentially from the ordinary form. There is a separate section on tetra-ethyl lead. The rarer metals, such as vanadium, are well described. The accounts of alcohols, ethers, aliphatic hydrocarbons and their halogenated derivatives, aromatic compounds, and organic solvents are all brief. They are not of much value for reference except that after each substance a useful list of the Italian literature (and some other references) is given. Unfortunately there is no indication of the incidence in Italy of poisoning caused by any of these substances, even in the case of lead.

The section which follows is devoted to allergic diseases ; conjunctivitis, allergic rhinitis, asthma, and skin conditions occurring in agricultural and chemical workers and caused by such materials as pollens, seeds, woods, skins, turpentine, and various oils and their derivatives. Allergy due to physical agents such as heat, cold, and various radiations is briefly described.

A few pages are devoted to occupational carcinoma, including a short account of skin cancers. There is no description of pitch warts ; lesions due to pitch and tar are rare in Italy owing to the small quantities of coal and its products which are used. Vesical and pulmonary carcinoma in relation to occupation are well described. Malignant conditions arising from luminising are briefly mentioned but no account of the important preventive measures is given.

The section on occupational skin diseases, by Dr. G. Farris, assistant in the dermatological clinic of the University of Genoa, is refreshingly different from most English accounts of the subject. After demolishing the Anglo-Saxon school which separates causative substances into the two main groups of primary irritants and sensitizing substances, Farris describes the skin lesions themselves in detail and works back to the occupational aetiology. This clinical approach produces an admirable and well balanced result. Under the aetiological groupings of mechanical, physical, chemical, and biological agents a wide variety of occupational skin conditions is described. In this classification there is little mention of " industrial dermatitis ", which clearly appears as a grouping of conditions for legal purposes rather than as an occupational disease entity in itself. The clinical approach of this article is to be commended. A brief account of preventive measures includes a reference to barrier creams, but no account is given of the different types of cream or the principles of their composition.

The book concludes with a chapter on fatigue and stress. There is a full discussion of the physiology and biochemistry of muscular work ; psychological aspects receive little mention. The syndrome of acute physical fatigue is described, with accounts of cardiovascular changes caused by exertion, including axillary vein thrombosis. In the respiratory system, emphysema and spontaneous pneumothorax caused by exertion are described. An account is given of effort albuminuria and skeletal changes of occupational origin. Miner's nystagmus is described and then follows an account of permissible hours of work and posture at work. Psychological aspects—the " will " to work—are not considered, nor are the so-called stress conditions affecting senior executives. Older and disabled workers and rehabilitation are not dealt with.

This new book will undoubtedly provide a useful general review of industrial medicine for general practitioners and senior students. From the above account it will be seen that many sections are dealt with in a somewhat different manner from that usually given in English textbooks ; the relative importance of different diseases is different in Italy. The author's clinical approach to the subject merits further attention in this country, but the book will be mainly of value here

because of the full lists of Italian (and some other) references given under each subject.

L. G. NORMAN

Ministry of Pensions and National Insurance. Digest of Statistics Analysing Certificates of Incapacity, 1950. (Pp. 14 ; 33 tables.)

Since the National Insurance Act came into force in July, 1948, the Ministry of National Insurance has collected much information on the nature and extent of sickness and injury forming the basis of claims for benefit. Some of this has been published in the Ministry's annual reports but additional information for 1950 has now been tabulated and distributed to those likely to be interested. It has not been officially published, partly because it is rather too specialized for the Ministry's annual reports, but more especially because, in the words of the report, " without an appreciation of the fields which they cover, and the sources of information on which they depend, they may be misinterpreted." For this reason it is important that deductions should not be made from the tables without due regard to the notes and definitions given. These explanations are given in a brief but very clear introduction ; the " working populations " covered by sickness and injury insurance are defined in detail, together with explanations of groups excluded, spells of illnesses not covered, age limits, etc.

" The statistics do not purport to give any measure of the morbidity of the whole population or of a representative sample of it." They are based for the most part on information obtained from random samples of persons receiving sickness or injury benefit and refer only to the insured working population. Hence, in general, there are excluded some 20,000 self-employed persons in small-income groups, members of the armed forces, non-industrial civil servants, and about half the married women in employment who have the choice whether or not to contribute towards sickness benefit. The approximate populations covered by these figures are :—

	Men	Women
Sickness	14,350,000	5,850,000
Injury	13,300,000	6,550,000

The number insured for injury is somewhat lower for men and higher for women, as self-employed persons are excluded for injury benefit while a proportion of employed married women choose to be excluded for sickness benefit.*

Benefit is not usually paid for spells of illness lasting less than four days, so that these short spells do not appear in the Ministry's figures. All breakdowns into causes of illness are based on the medical certificates, furnished in support of claims to benefit, and " not always indicated with precision ". " Now that the certificates are being used as a basis for these statistics, it is very much hoped that practitioners will appreciate the importance of showing on each certificate the cause of incapacity as accurately as they know it at the time of issue. As the standard of precision of certification improves, so will the value of the statistics increase." In 1950 there were approximately 7½ million spells of certified incapacity due to sickness or injury totalling about 200 million lost working days. Just over 10% of the spells were due to accidents or prescribed diseases. The tables relating to injury benefit do not include much of the time lost in long term injury cases since injury benefit is in no case paid for more than six months from the date of the accident or development of the prescribed disease. Benefit for pneumoconiosis and byssinosis does not normally appear in the industrial injury tables.

Some idea of the field covered can be obtained from the following summary of the tables. Figures for sickness benefit are given for different areas for " new claims " starting in 1950 together with the number of days of incapacity for spells of sickness. The latter is also given in fuller detail for men and women separately according to age and cause, with total and median duration, etc. Injury benefit figures are shown in similar detail separately for industrial accidents and for prescribed diseases. These are also analysed by site of injury and by industry or occupation. Unfortunately, no analyses of the populations at risk by industry or occupation are available, although age analyses are included. (The 1% tables of the 1951 census give a breakdown of the total population by occupation but for some occupations this varies considerably from their insured populations.)

For anyone interested in obtaining this report or in receiving further explanation on any aspect, contact should be made with the Medical Department or the Statistics Division of the Ministry of Pensions and National Insurance at 10, John Adam Street, London, W.C.2.

NANCY GOODMAN

Review of Pneumoconiosis Abstracts, Vol. I. (Reprinted from the *Bulletin of Hygiene* for the years 1926 to 1938 inclusive), with Foreword by Charles Wilcocks, Director of the Bureau of Hygiene and Tropical Diseases. (Pp. xi + 347 ; illustrated. 63*s*.) London : Sir Isaac Pitman. 1953.

All those who are familiar with the *Bulletin of Hygiene* will welcome this collection of abstracts on pneumoconiosis. The original suggestion that such a collection should be made was put forward by Professor E. J. King, and the work of selecting the relevant abstracts was carried out by Dr. E. L. Middleton. The result is a miniature history of the subject which is of great interest and value. Abstractors in the *Bulletin of Hygiene* are always careful to give a fair idea of the content and value of the paper reviewed. Anyone coming fresh to the subject, and wishing to acquire a thorough knowledge of it in the shortest possible time could not do better than read this book. We look forward to the second volume, which will bring the history up to 1950, with the keenest anticipation.

B. M. WRIGHT

* The population of Great Britain is approximately 15¾ million men aged 15–65 and 15½ million women 15–60. This includes members of the armed forces actually in the country.

The Art of Scientific Investigation. By W. I. B. Beveridge. Second edition. (Pp. xii + 176; illustrated. 10*s.* 6*d.*) London: William Heinemann Ltd. 1953.

A second edition of this admirable book will be welcomed by anyone who wants to understand the mental attitudes and processes by which scientists have made their great discoveries during the past three centuries. The author is Professor of Animal Pathology at Cambridge and his own experience of biological research gives the book a strong bias towards this and neighbouring branches of science, although he also quotes the views of eminent physicists and mathematicians. His purpose is to summarize and systematize what has been recorded of the mental skills required for scientific research by analysis of the methods that successful investigators appear to have employed. He is not concerned with the logic or philosophy so much as the psychology and practice of research. Nor, of course, does he discuss technology except to admit the necessity for technical training in most branches of science.

The picture of scientific method that emerges may surprise those who have neither known scientists personally nor studied their biographies, but who have learnt their science from lectures, textbooks, and published papers. In such presentations, experiment appears to lead inexorably to hypothesis and so to further experiment, and the ultimate conclusion appears to be reached by a course of immaculate logic. The actual course of discovery is actually quite different. The chance observation of an astute observer or the leap of intuition leads to an hypothesis that can be put to experimental proof. Many false hypotheses may be rejected on the way to the discovery of the truth. The final account of the success conceals the false trails that led Kelvin, for instance, to describe his efforts for the advancement of science during 55 years by the one word "failure".

Among the characteristics essential for research, the author includes insatiable curiosity, powers of observation, freedom from prejudice, and determination. The necessary conditions are leisure for thought, opportunities for observation, experiment, reading, and discussion.

The strategy and tactics of research, the difficulties that may be met, and the rewards that may be found, are all described with ample illustrations from the experience of scientists. Every young research worker should read this book and anyone attempting research, on whatever scale, will find wisdom and encouragement here.

It is an impressionistic sketch rather than a philosophic treatise and it has a slightly disjointed style, which no doubt reflects the original jottings from which the author admits it was compiled. Whether it is dipped into, or read consecutively, it will be greatly enjoyed and will help and interest a lot of people.

C. M. FLETCHER

THE JANUARY (1954) ISSUE

The January (1954) issue contains the following papers :—

ε-Caprolactam. By M. W. Goldblatt, Muriel E. Farquharson, Geoffrey Bennett, and Beryl M. Askew.

The Reaction of Rats to Diets Containing Octamethyl Pyrophosphoramide (Schradan) and 00-Diethyl-S-Ethylmercaptoethanol Thiophosphate ("Systox"). By J. M. Barnes and F. A. Denz.

Sickness Absence before the First Clinical Episode of Coronary Heart Disease. By J. A. Heady, J. N. Morris, F. J. Lloyd, and P. A. B. Raffle.

Pilot Trial of an Antihistaminic Drug in the Control of "Tetryl" Dermatitis. By W. A. Bain and Grizel H. Thomson.

Perforation of the Nasal Septum due to Soda Ash. By R. McL. Archibald.

The Effect of the Drinking Pattern on Water Economy in Hot, Humid Environments. By R. A. Kenney.

The Mill Reek and the Devonshire Colic. By Andrew Meiklejohn.

Miscellanea :

Beryllium Granuloma of the Skin. By Henry Lederer and John Savage.

First Conference of the British Occupational Hygiene Society

Occupational Hygiene in Great Britain. By Thomas Bedford.
Measuring the Workers' Environment. By S. A. Roach.
The Problem of Chemical Toxicity. By D. G. Harvey.
Occupational Hygiene and the Industrial Designer. By J. E. Braham.

Book Reviews.

Abstracts.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the abstracting journal,* Abstracts of World Medicine, *published by the British Medical Association. The abstracts are divided into the following sections: toxicology; industrial physiology; industrial lung disease; industrial skin diseases; accidents and orthopaedic surgery; industrial ophthalmology; environment; general. Not all sections will necessarily be represented in any one issue)*

INDUSTRIAL TOXICOLOGY

Antidotal Efficacy of Vitamin B_{12a} (Hydroxocobalamin) in Experimental Cyanide Poisoning. MUSHETT, C. W., KELLEY, K. L., BOXER, G. E., and RICKARDS, J. C. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **81**, 234.

The addition of cyanide ions to a solution of vitamin B_{12a} (hydroxocobalamin) results in the formation of vitamin B_{12} (cyanocobalamin). The cyano group is tightly bound to the cobalt atom and the process is apparently irreversible, for vitamin B_{12} is non-toxic to mice even when given in doses up to 1,600 mg. per kg. body weight intravenously and intraperitoneally, a dose which contains the equivalent of 32 mg. of cyanide ion per kg., which is about 8 times the LD100 dose. These observations suggest that vitamin B_{12a} might be of value as an antidote to cyanide, and this has been confirmed by the authors in a series of experiments on mice carried out at the Merck Institute, Rahway, New Jersey, in which it was shown that vitamin B_{12a}, administered intravenously, is capable both of preventing and of reversing the effects of the intraperitoneal injection of aqueous solutions of potassium cyanide.

For prophylaxis, a dose of 50 or 250 mg. of vitamin B_{12a} per kg. given 20 seconds before the cyanide injection gave adequate protection against doses of 5·5 to 8·0 mg. per kg. In treatment an intravenous dose of 250 mg. of vitamin B_{12a} per kg. given within one or two minutes, or of 100 mg. per kg. within one minute, of the intraperitoneal injection of 10 mg. of potassium cyanide per kg. (a lethal dose) caused the immediate disappearance of respiratory distress and convulsions and prevented death. Given 6 to 8 minutes after the injection of potassium cyanide, vitamin B_{12a} was ineffectual. However, mice "apparently dead" of cyanide poisoning reacted dramatically to the injection of vitamin B_{12a} within 2 to $3\frac{1}{2}$ minutes of the cyanide injection, 7 out of 21 recovering.

In a study of the metabolism of cyanide and vitamin B_{12a} each of 6 mice was poisoned by the intraperitoneal injection of 10 mg. of potassium cyanide per kg., and approximately one minute later each was given an intravenous injection of 100 mg. of vitamin B_{12a} per kg. The urine was collected during the next $2\frac{1}{2}$ hours and it was found that 9·6% of the cyanide given was excreted in the urine during this period in the form of cyanocobalamin, 0·7% as free cyanide, and 3·5% as thiocyanate.

M. A. Dobbin Crawford.

INDUSTRIAL LUNG DISEASES

Silicotic and Tuberculosilicotic Lesions Simulating Bronchiogenic Carcinoma. KERGIN, F. G. (1952). *J. thorac. Surg.*, **24**, 545.

In this paper from the General Hospital and University of Toronto the author describes 8 cases in which radiological abnormalities showing collapse with consolidation of one or more pulmonary segments suggested the diagnosis of bronchial carcinoma. The patients had all had a recent illness with increased cough and sputum and, in 4 cases, haemoptysis. In one there was a definite history of silicosis, and the diagnosis of conglomerate silicosis was made. In the other 7 patients, despite negative results on bronchoscopy, thoracotomy was carried out, with pneumonectomy in 4 cases, lobotomy in 1, and biopsy alone in the other. In every case the pathological findings confirmed the presence of silicosis (with added tuberculosis in 2 cases). Enlarged silicotic hilar lymph nodes had apparently resulted in secondary chronic pneumonitis as a result of atelectasis in one or more segments of the lung. In 3 of the cases subjected to pneumonectomy pathological examination revealed discrete silicotic nodules throughout the lung despite the absence of nodular shadows in the radiograph. The patients' recent symptoms were relieved after operation, but shortness of breath appears to have been increased.

The author concludes that in these cases it is impossible to reach a preoperative diagnosis of silicosis, so that thoracotomy is necessary. Because of the extensive fibrosis, lobectomy is seldom possible and pneumonectomy has to be carried out.

(The chief interest of this paper is the demonstration of the development of a silicotic type of fibrosis as a result of non-specific infection in atelectatic pulmonary segments. The tuberculous infection in 2 cases was thought to be secondary. The merits of resection, once the diagnosis has been made at thoracotomy, are not clearly established.) *C. M. Fletcher.*

The Mortality from Phthisis and its Related Factors in Young Women in England and Wales. A Cohort Study Based on the Period 1851–1938. RUSSELL, W. T. (1952). *Med. Offr.*, **88**, 269.

In this paper from the Institute of Social Medicine, Oxford, the author discusses methods of correlating age and disease, and points out that to base this correlation on one calendar year conveys a misleading impression and that it is statistically sounder to base it on a study by cohort or generation.

From the annual number of female births in England and Wales for the period 1851–1922 and the female deaths for the period 1851–1938, the probability was calculated of a female aged 0, 5, 10, 15, 20, 25, 30, or 35 years, born in a particular triennial period, dying within 5 years from pulmonary tuberculosis. In addition, life-tables were constructed showing the number of females born in successive triennial periods from 1851–1922 who survived to adult age. Of those born in the first period, 1851–3 (that is, Cohort 1), 68% reached the age of 25 and 59% reached 45. There was a steady improvement up to Cohort 11 (1881–3) when the figures were 75% and 70% respectively. There was no improvement for the next five cohorts (1884–98), after which there was again a steady rise. This stationary period is attributed, in the main, to the heavy mortality from epidemic diarrhoea among children at this epoch and secondarily to the effect of the first world war and the influenza epidemic of 1918–19. For Cohort 1, of each 1,000 females born, 100 died from phthisis before the age of 45, of whom 47 died under the age of 25. For Cohort 11 (30 years later), the figures were 41 and 18 respectively, showing that progress has been made in the reduction of the mortality from pulmonary tuberculosis.

Tables giving the probability of dying within 5 years from pulmonary tuberculosis at a given age and cohort show that the age of maximum mortality was 20, tending towards age 25, in the period 1851–77 (Cohorts 1 to 9); for the next 15 years it rose higher until 1892 (Cohort 14), after which it then reverted to age 20 and in 1912–14 was tending towards age 15. Correlation coefficients were calculated in pairs between (1) the probability of dying within 15 years after birth from all causes other than phthisis (that is, "childhood environment"), (2) the probability of dying within 15 years after birth from any form of tuberculosis (that is, childhood tuberculous infection), (3) the probability of dying within 5 years from all causes except phthisis, at ages 15, 20, 25, 30, and 35 (that is, "adult environment"), and (4) the probability of dying within 5 years from phthisis at ages 15, 20, 25, 30, and 35 (that is, the observed mortality from phthisis).

These calculations show that the mortality from phthisis of any female generation below 25 is related to the childhood environment. For the survivors beyond 25 the adult environment is the important factor. There is no evidence of any association between childhood infection and the mortality from phthisis in young adults.

M. Lubran.

GENERAL

Whale Finger and Seal Finger: their Relation to Erysipeloid. HILLENBRAND, F. K. M. (1953). *Lancet*, **1**, 680.

In this short paper from the Falkland Islands the author reviews some of the literature on erysipeloid (Baker–Rosenbach) and discusses his experience of hand infections in workers in the whaling and sealing industries in South Georgia, the Falklands Islands, and in the Antarctic.

The terms "whale finger" and "seal finger" are used locally to describe the infective lesions which occur as occupational hazards. In the whaling industry most hand infections are digital and are caused by minor cuts and abrasions from the handling of frayed steel ropes to which cling fragments of whale meat. Among sealers infections develop following cuts from the knife used in dealing with carcases.

The author analyses 66 cases of infection of the hands, chiefly following lesions on the volar surface of the index and middle fingers, which were seen between April, 1950, and March, 1951. Of 60 cases among whalers, 41 were of cellulitis and 9 of erysipeloid, while of 6 cases in sealers 2 were of erysipeloid. In 3 instances cellulitis and erysipeloid were found in the same patient. The author believes that there would have been further cases of erysipeloid if cellulitis had not been promptly treated when it occurred.

From observation in 4 cases the incubation period for erysipeloid was considered to be 2 to 3 days. No spread to other fingers was observed, nor was any generalized or intestinal form of erysipeloid seen. One case was complicated by cubital lymphadenitis and one by septic arthritis. The author's facilities for bacteriological investigation were very limited; in no case was *Erysipelothrix rhusiopathiae* isolated.

Treatment in early cases consisted in immobilization and local application of 30% mercury ointment, penicillin being reserved for cases with complications.

Benjamin Schwartz.

Special Seating for Workers with Disabilities of the Lower Limbs. TALITSKY, B. N. (1952). *Gigiena*, 31, No. 12.

The author points out that fatigue and waste of energy are caused when workers perform their tasks in awkward and uncomfortable positions, and gives examples of special seats designed for disabled workers with deformities of the lower limbs, including persons with amputation through the thigh and knee and those with ankylosed joints. These seats can be adjusted to suit the individual and enable him to work in the most convenient and comfortable position.

(A study of the original article is recommended to those who are interested in such problems, as the designs can only be understood by reference to the photographs and diagrams reproduced.) *L. Firman-Edwards.*

Brit. J. industr. Med., 1954, **11**, 167.

SOME TOXIC PROPERTIES OF DIMETHYLNITROSAMINE

BY

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(RECEIVED FOR PUBLICATION MAY 22, 1954)

The appearance of two cases of cirrhosis of the liver among three men working in the research laboratory of a large industrial undertaking led to suspicion becoming attached to dimethylnitrosamine (D.M.N.) as the causative agent. Dimethylnitrosamine had been introduced into the laboratory as a solvent about 10 months before the first case of cirrhosis was discovered. One of the men had died of bronchopneumonia, and cirrhosis of the liver was an incidental finding at necropsy. The second man with a long-standing history of dyspepsia had a laparotomy after five months' exposure to D.M.N. At that time no note of any abnormality of the liver was made. Six months later he was examined for an incisional hernia that had developed in the operation scar. It was then recorded that the liver felt hard and was suspected of being cirrhotic. Liver function tests carried out at this time showed evidence of damage. When repeated three months later after all further exposure to D.M.N. had ceased these tests indicated an improved liver function. The third man has remained in good health but has had no liver function tests carried out on him.

A search of the literature revealed only a single short report of the toxic properties of D.M.N. (Hamilton and Hardy, 1949). Dimethylnitrosamine had been used in an automobile factory and some illness had followed. Experiments on dogs showed it to be capable of producing severe liver injury, but no experimental details are provided. The medical officer of the firm therefore asked if we would examine the toxic properties of D.M.N. towards laboratory animals.

Dimethylnitrosamine, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!N.NO$, is a mobile yellow liquid with a faint, characteristic odour. It boils at 151° C. and its specific gravity is 1·015 at 20° C. It is miscible in all proportions with water, ethyl alcohol, methylene chloride, or vegetable oil. Under ordinary conditions it is a stable substance, but with zinc dust and acetic acid it can be reduced to dimethylhydrazine $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!N.NH_2$.

Preliminary experiments revealed that D.M.N. readily produced a severe liver injury and this paper gives an account of some of the features of the lesions.

Materials and Methods

The D.M.N. was a sample of pure material specially prepared by the firm who had both made and used the D.M.N.

Male and female albino rats were used in the majority of the experiments. Additional observations were made on mice, guinea-pigs, rabbits, and dogs.

For single oral doses a solution of D.M.N. in water was administered. For injection either an aqueous solution was used or the undiluted D.M.N. was given by a micro-syringe. Percutaneous absorption was studied on rats depilated with barium sulphide. The D.M.N. was applied undiluted and the skin left uncovered. The rats were placed in small individual wire cages for four hours after each dose so that they could not lick themselves.

For the feeding experiments solutions of D.M.N. were made up in arachis oil. These solutions were added at the rate of 10 ml./kg. of powdered rat diet (M.R.C. diet 41).

For histological work animals were killed with coal gas unless already dead. Tissues were fixed in 10% formol-saline and in Helly's fluid. Paraffin sections cut at 7μ were stained by haematoxylin and eosin, by the van Gieson and the Mallory azocarmine methods for connective tissue, Gomori's silver method for reticulin, and by the periodic-acid-Schiff technique (McManus, 1946). Frozen sections of material fixed in formol-saline were stained with Sudan IV. Sections of pancreas, after fixation in Bouin's fluid, were stained by the aldehyde fuchsin and the chromium haematoxylin phloxin methods (Gomori, 1941, 1950).

Results

Acute Poisoning.—In all species examined a single lethal dose of D.M.N. by mouth or by injection

produced extensive liver necrosis but the differences in the reactions of each species merit a separate description.

Rats.—The L.D. 50 by intraperitoneal injection was 26·5 (20·5–34·2) mg./kg. calculating the results by the method of Weil (1952). Although the response of rats to an oral dose varied somewhat in different experiments, the average lethal dose was less than 50 mg./kg. The rats never died in less than two days or more than six days after a single oral dose. They appeared ill, sitting quietly with ruffled coats, but displayed no other sign of poisoning except that abdominal swelling was visible in some animals surviving several days.

At necropsy there was a variable amount of blood-stained fluid in the peritoneal cavity. The volume might exceed 30 ml. and sometimes had a colour and consistency approaching that of pure blood. The omentum and pancreas often had a jelly-like oedema in their interstices, and subcutaneous oedema over the abdominal wall was occasionally seen. Haemorrhage into the lumen of the upper part of the intestine was sometimes observed. The liver was swollen, dark and mottled, and somewhat friable. Apart from a little clear pericardial and pleural exudate in some animals there were no other lesions visible to naked-eye examination. Haemorrhage was confined to the peritoneal cavity and lumen of the gut. In a number of animals where this was pronounced, the possibility that cerebral haemorrhage might have occurred was excluded by direct examination.

A dose of 40 to 50 mg./kg. had a similar effect whether given by mouth, by intravenous, intraperitoneal, or subcutaneous injection. But acute poisoning could not be produced by percutaneous application of undiluted D.M.N. A dose of 100 mg./kg. applied on four successive days had no effect on the general condition of six rats.

Rabbits.—A dose of 15 mg./kg. killed rabbits in less than 24 hours. Those given 10 mg./kg. either died in less than 24 hours or survived at least 10 days. A straw-coloured peritoneal exudate was usually present at death but it was never haemorrhagic. The liver was large, dark, and friable but no other lesions were visible to naked-eye examination.

Mice.—Mice behaved like rabbits. Death always took place within 30 hours and all mice receiving 20 mg./kg. died. Any peritoneal fluid present at death was clear. The livers were swollen, red, and mottled.

Guinea-pigs.—Eight animals receiving doses of 25 to 50 mg./kg. all died, but none in less than four days or more than eight days after the D.M.N. In the majority a haemorrhagic peritoneal exudate was present at death and the liver was congested and mottled.

Dogs.—One dog was given a single oral dose of 50 mg./kg. An hour later it vomited several times. Next morning it was conscious but unable to stand and died quietly 20 hours after receiving the D.M.N. At necropsy the peritoneum contained about 100 ml. of bright red blood and the stomach and gut were full of blood, some obviously recently shed. There were no other lesions or haemorrhages. The liver was not grossly abnormal to naked-eye examination.

A second dog died in less than 24 hours after a single oral dose of 20 mg./kg. Again it vomited repeatedly soon after the D.M.N. Within six hours it was comatose though moved when touched. At necropsy there was no peritoneal haemorrhage but the stomach and upper parts of the gut contained much bright red blood. The liver appeared congested.

A third dog received 10 mg./kg. by mouth on three separate occasions. Eight days elapsed between the first and second doses and four days between the second and third. It vomited about an hour after the first two doses. It was not obviously ill until the seventh day after the last dose, when it was found unconscious in the morning. At necropsy there was about 100 ml. of fluid resembling pure blood in the peritoneal cavity. The stomach and small intestine contained a black fluid and the bowel contained typical melaena. There were no erosions in the stomach. The mesenteric lymph nodes were red. The liver was firm and tense ; the cut surface was mottled and had a " nutmeg " appearance. There was no obstruction or gross lesion within the lumen of the hepatic vein. The pleural and pericardial cavities and the lungs were healthy.

Subacute Effects.—Rats that lived for seven days or more after a dose of 20 to 40 mg./kg. frequently appeared ill and ate little. They had a pronounced abdominal swelling due to fluid that could be aspirated. This fluid accumulation masked any loss of weight due to emaciation. The liver was of variable size and often irregular in outline. In some animals it showed evidence of fibrosis.

Two rabbits surviving a dose of 10 mg./kg. appeared ill 10 days later and at necropsy both had some peritoneal exudate and small, symmetrically shrunken livers.

Chronic Poisoning.—Chronic poisoning was produced by giving a diet containing 50, 100, and 200 parts per million (p.p.m.) D.M.N. to groups

of six young rats. The reactions of the groups were as follows :—

50 *p.p.m.*—After 110 days on the diet the mean weight of the group on D.M.N. was significantly lower than that of the control group. No rats died nor was anything abnormal noted at necropsy on those killed at this time.

100 *p.p.m.*—All the rats died after 62 to 95 days on the diet. At 60 days the mean weight of the group was only 65% of that of the controls.

200 *p.p.m.*—All rats died or were killed *in extremis* after 34 to 37 days on the diet. At necropsy all rats in the last two groups showed extreme emaciation and complete absence of body fat. The food intake was unaffected during the first two weeks on these diets indicating that D.M.N. in the concentration used did not reduce the palatability of the diet. Emaciation must have been the result of the toxic effects of D.M.N. Gross peritoneal exudate was not seen in these animals but in some there was evidence of recent haemorrhage into the gut. The retroperitoneal and retrosternal lymph glands were sometimes red. The liver was small and in those dying later there was obvious fibrosis. The pleural surfaces of the lungs often showed a number of discrete brown stains scattered over them.

Histological Observations

Liver.—A detailed account of the changes seen in the rat is given and findings in the other species briefly compared. A single dose of 5 to 10 mg. D.M.N./kg. produced no significant damage, but a dose of 20 mg./kg. or above led to characteristic changes. Within six hours there was a pallor of the centrilobular and midzone regions where the liver cells showed an eosinophilia of the cytoplasm greater than in those cells in the periportal zones. The central veins were moderately congested and the sinusoids dilated. Fat staining showed a deposition of fine sudanophilic droplets in the cells of the centrilobular areas. In the same area glycogen was depleted.

At 18 hours the changes were more conspicuous though still confined to the centrilobular and midzone regions. The parenchymal cells were obviously damaged. The cytoplasm was amorphous and eosinophilic, frequently vacuolated but only rarely to the extent of producing large hydropic cells (Fig. 1). The nuclei were swollen, pale and irregular in outline. The periportal zone and portal tracts were unaffected. The contrast was more striking in sections stained for fat. The periportal areas were free from any deposit of sudanophilic material (Fig. 2). Glycogen was almost completely absent.

By 24 hours the necrosis of the centrilobular and midzone cells was general. The necrotic areas were becoming confluent and haemorrhage into them was frequent. The isolated periportal areas of apparently healthy liver cells were surrounded by bands of congested necrotic tissue. The reticular framework remained intact.

By 48 hours this pseudo-lobular appearance was very marked (Fig. 3) and the necrotic bands were haemorrhagic. The red blood cells showed evidence of degeneration. There was an early invasion of the damaged area by polymorphonuclear cells. The proportion of necrotic to apparently healthy tissue varied considerably from animal to animal but the general picture was the same. By this time active regeneration as witnessed by numerous mitotic figures and binucleate cells had started (Fig. 4). The reticular pattern was preserved but the reticulo-endothelial cells were swollen and deeply stained but not obviously damaged. The portal tracts were normal.

By 72 hours the areas of necrosis had begun to shrink and were separated from the regenerating parenchyma by empty clefts (probably artefacts) (Fig. 5). This gave the lesions a " punched out " appearance. The necrotic areas contained only polymorphs and reticulo-endothelial cells among the debris and a few nuclear remnants from the parenchymal cells. The reticulin framework and the central veins were intact (Figs. 6 and 7).

Sections from animals killed at a later stage were almost certainly from animals that would have ultimately survived. The picture was very variable depending as it must upon the extent of the original injury. There was a progressive shrinkage of the necrotic areas and its replacement by actively growing liver cells from the undamaged areas. At first the regenerated areas showed irregular arrangement of the cells but by 17 days the liver had almost regained its normal appearance with only occasional fine strands of young connective tissue as a reminder of the pre-existing necrosis. In one animal killed 17 days after a dose of 45 mg./kg. there was evidence of incomplete repair with persistent islands of necrosis and more prominent branches of young connective tissue.

The livers of rats dying while being fed diets containing 200 and 100 p.p.m. of D.M.N. showed a similar picture of acute liver injury with considerable variation in degree from animal to animal. The islands of periportal tissue often contained parenchymal cells with unusual nuclear forms but rarely showing mitosis. There was little fatty change and glycogen was always absent. The bands of necrotic tissue might show variation in the proportion

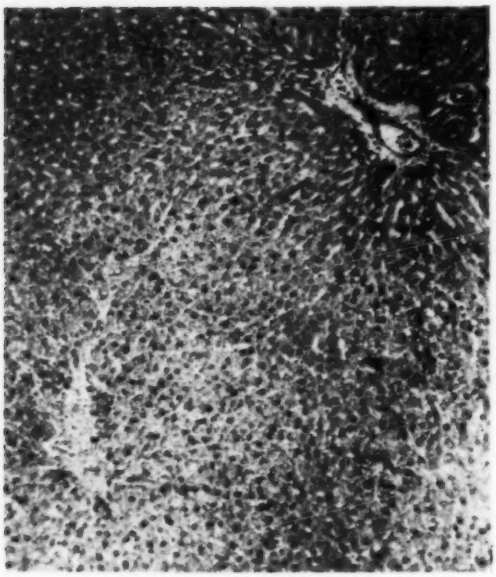

FIG. 1.—Rat liver after ingestion of D.M.N., 50 mg. per kg., for 18 hours. Haematoxylin and eosin. Early centrilobular and midzonal necrosis. × 100.

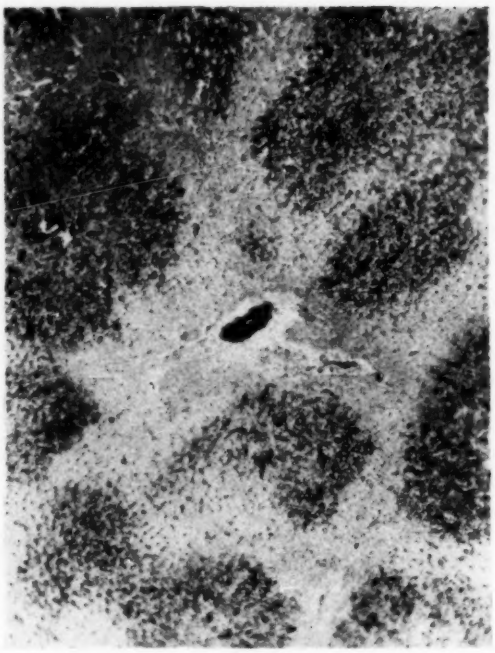

FIG. 2.—Rat liver after ingestion of D.M.N., 50 mg. per kg., for 18 hours. Sudan IV green filter. The pale areas represent surviving periportal parenchyma: the darker areas represent the necrotic zones containing many sudanophil droplets. × 60.

FIG. 3.—Rat liver after ingestion of D.M.N., 30 mg. per kg., for 48 hours. Haematoxylin and eosin. The darker areas of surviving periportal parenchyma are isolated by large confluent zones of necrosis. × 18.

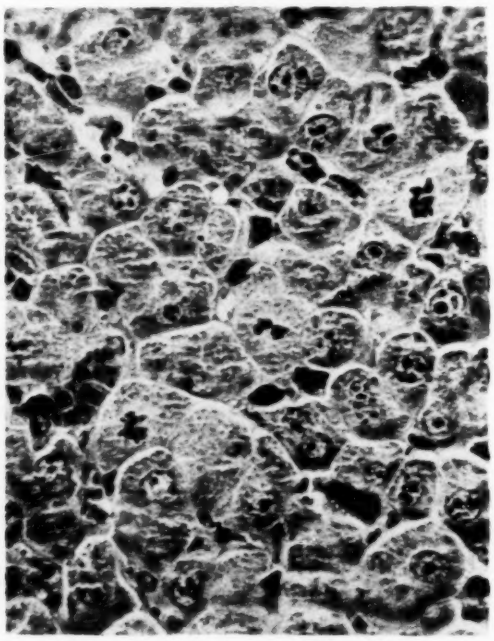

FIG. 4.—Rat liver after ingestion of D.M.N., 30 mg. per kg., for 48 hours. Haematoxylin and eosin. Regenerating parenchymal cells with three mitotic figures. × 500.

FIG. 5.—Rat liver after ingestion of D.M.N., 50 mg. per kg., for 72 hours. Haematoxylin and eosin. The necrotic zones are abruptly demarcated from the regenerating parenchyma. × 60.

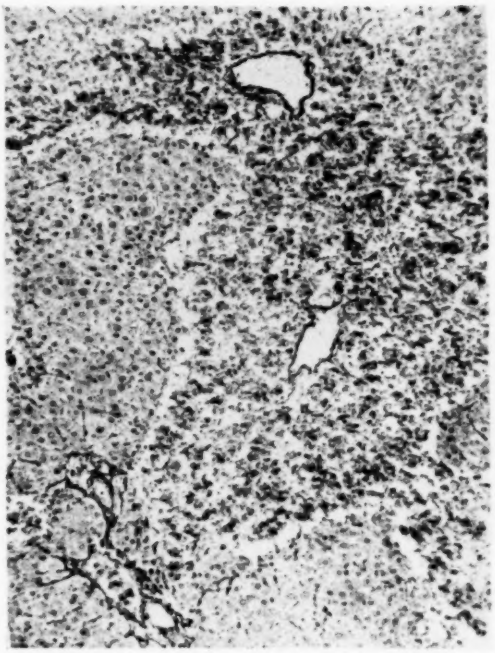

FIG. 6.—Rat liver after ingestion of D.M.N., 50 mg. per kg., for 72 hours. Gomori silver impregnation. The reticular network persists in the necrotic area with no obvious reduction in the distance between the hepatic vein and the portal tract. × 100.

of its different constituents—degenerating hepatic cells, red cells and red-cell debris, macrophages, fibroblasts, and young connective tissue (Fig. 8).

In those surviving longest there was some bile duct proliferation and more fibrous tissue (Fig. 9). There was often a deposit of a yellow pigment staining for iron.

A histological picture similar to that in the rat was seen in the liver of the dog, with typical centrilobular haemorrhagic necrosis extending out into the mid-zones and leaving only narrow rims of surviving parenchyma around the portal tracts. The portal veins showed severe congestion and dilatation and there was frequent haemorrhage into the connective tissue of the portal tracts. The lymphatics of the portal tracts were widely dilated. The hepatic veins were patent. In the rabbits and mice there was less evidence of a zonal injury to the liver lobules and the effect more closely resembled that of a massive necrosis (Himsworth, 1947). In neither species did animals survive more than 30 hours after the administration of D.M.N.

Other Organs.—These showed little change. The lungs were congested and sometimes showed small

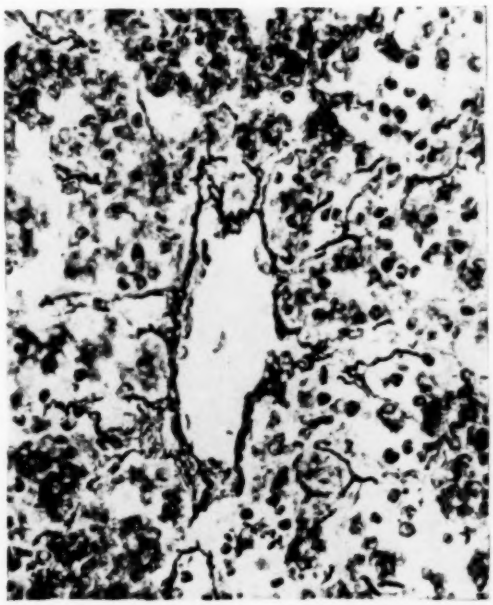

FIG. 7.—Rat liver after ingestion of D.M.N., 50 mg. per kg., for 72 hours. Gomori silver impregnation. Same preparation as Fig. 6 to show intact central vein, also persisting reticular strands in the necrotic tissue. × 400.

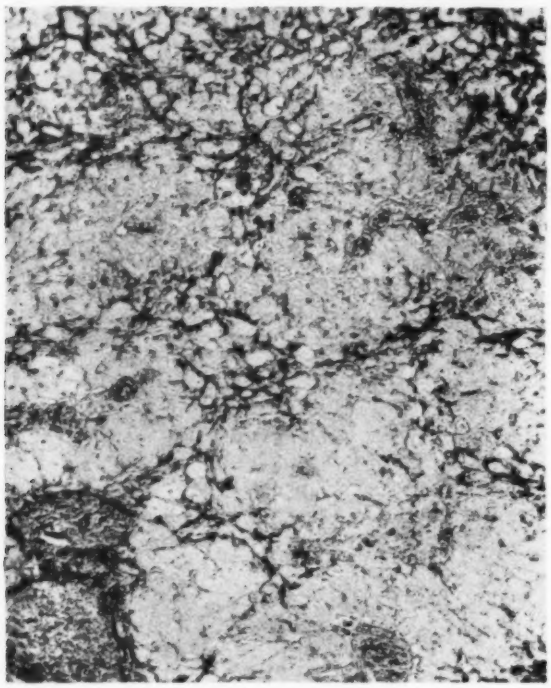

FIG. 8.—Rat liver after ingestion of D.M.N., 100 p.p.m., for nine weeks. Mallory's azocarmine. Irregular formation of fibrous tissue. × 100.

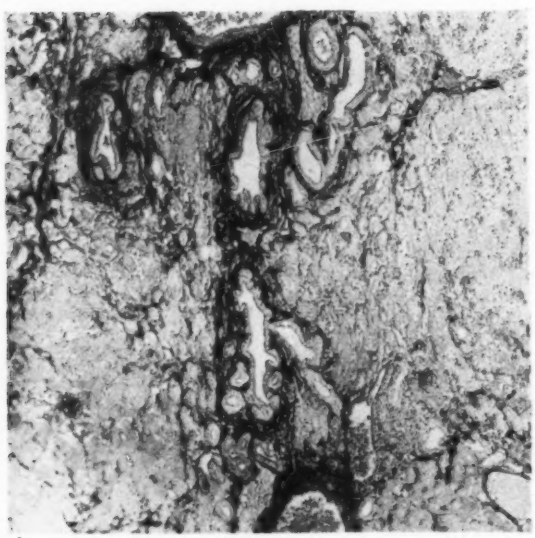

FIG. 9.—Rat liver after ingestion of D.M.N., 100 p.p.m., for nine weeks. Mallory's azocarmine. Same preparation as Fig. 8 showing fibrous tissue and bile duct proliferation. × 100.

haemorrhagic areas. The kidneys were normal. The spleen had a reduced red cell content and a more prominent reticulo-endothelial component. The retrosternal lymph glands contained amorphous eosinophilic debris, degenerating erythrocytes and macrophages filled with yellow-brown pigment. In the dog there was no evidence of congestion in the gastro-intestinal tract and the mucous membrane was well preserved.

Discussion

Dimethylnitrosamine appears to act primarily as a liver poison producing severe liver necrosis in rats, mice, rabbits, guinea-pigs, and dogs. The species examined seem to be more or less equally susceptible to D.M.N. and the general picture of poisoning is consistent with that following a severe liver injury. Some features of the condition merit further discussion.

The haemorrhagic peritoneal exudate and the bleeding into the lumen of the gut are striking features of poisoning in rats, dogs, and guinea-pigs. It has not been described in animals with liver injury following carbon tetrachloride, beryllium, phosphorus, or diphtheria toxin, for example. However, poisoning by senecio (ragwort) can produce liver damage and internal haemorrhage in horses and cattle and the condition has been produced experimentally in rats (Davidson, 1935). Although the loss of blood may be a contributory cause of death after D.M.N. in those species in which it occurs, death is just as rapid in those species in which there is no haemorrhage. Dimethylnitrosamine produces no histological evidence of widespread damage to any important organ other than the liver. The congestion and other signs of injury in the lungs were probably terminal.

Like carbon tetrachloride, D.M.N. produces a centrilobular necrosis and complete recovery is possible after the extensive damage produced by a single near-lethal dose. Repeated doses, as in the feeding experiment, may lead to fibrosis. However, the lesions due to D.M.N. differ from those due to carbon tetrachloride in that they are haemorrhagic and show a sharp transition from the damaged to undamaged liver tissue. In the central part of the lobule the hepatic cells appear totally destroyed while at the periphery they appear normal. The swollen hydropic or otherwise apparently injured liver cells are rarely seen after D.M.N.

In some respects the distribution of the lesions gives the liver the nutmeg appearance associated with passive venous congestion. In dogs a centrilobular necrosis that resembles the lesions of chloroform poisoning has been described after temporary

ligation of the hepatic vein (Simonds and Callaway, 1932). In cats and monkeys similar lesions have been described after experimentally produced chronic venous congestion (Bolton, 1914–15). Permanent partial occlusion of the hepatic vein in dogs leads to death within 72 hours if the occlusion is too severe (Zimmerman and Hillsman, 1930). Two of three dogs so dying had a serosanguineous peritoneal exudate and pools of blood were present throughout the greater part of the liver lobules, but no detailed histological descriptions were given.

In rats poisoned with senecio (Davidson, 1935) the lesions are very similar to those produced by D.M.N. and there was an accompanying oedema of the parietal peritoneum. Histologically in both cases there was a sharp line of demarcation between the healthy and necrotic tissue. In senecio poisoning, however, the central veins of the liver lobules were frequently seen to have been ruptured and there was endothelial proliferation of the hepatic and pulmonary veins. Such changes were not seen in rats poisoned with D.M.N.

The cause of the haemorrhages into both the injured liver and the peritoneal cavity and lumen of the gut is not apparent. The lungs may be the seat of small haemorrhages but otherwise there seems to be no general tendency to haemorrhage outside the area draining into the portal veins.

A striking feature of the liver lesion in rats poisoned with D.M.N. is the sharp line of demarcation between the totally destroyed parenchyma and apparently uninjured liver cells. This may indicate a short-lived action of a severe, rapidly acting poison. The fact that D.M.N. is freely soluble in water means that it would probably be excreted rapidly if not quickly metabolized and broken down in the body. In the rabbit death takes place rapidly even after a dose of D.M.N. that is just lethal. In this species, few if any liver cells seem to be spared.

The way in which D.M.N. damages the liver cannot yet be surmised. If it is a rapidly acting poison it might be assumed that after oral administration the gut, portal vessels, and liver are directly damaged by the passage of D.M.N. during its absorption. The fact that similar lesions can follow the intravenous administration of D.M.N. suggests that these tissues possess some unusual susceptibility to the toxic action of D.M.N. The tendency to haemorrhage in certain species may be the result of some impairment of blood clotting-mechanisms or to action on blood vessels. If the latter is the case the peculiar distribution of the lesions might be the result of an accentuation of venous back pressure in the portal system as a sequel to the injurious action of D.M.N. on the liver. In the dog the lesions in the liver are very similar to those described in dogs killed during anaphylactic shock (Dean and Webb, 1924). On the other hand a careful examination of the intestinal mucosa in the dogs poisoned by D.M.N. failed to reveal any of the intestinal lesions said to accompany anaphylaxis in this species (Manwaring, Beattie, and McBride, 1923).

Turning to the possible chemical mechanisms whereby D.M.N. exerts its toxic action, there is again no evidence as to how this is brought about. It is conceivable that D.M.N. might be reduced, by circulating or intracellular sulphydryl groups, for example, to dimethylhydrazine. Hydrazine itself produces liver necrosis but spares other tissues (Wells, 1908).

However, preliminary observations in this laboratory by W. N. Aldridge have shown that rabbits given dimethylhydrazine die in convulsions 24–48 hours after a dose of 100 mg./kg. without histological evidence of any liver damage. Bodansky (1924) examined a number of substituted hydrazines, not however including dimethylhydrazine, and found that not all of them damaged the liver.

There remain therefore three possibilities to consider in further work on D.M.N. Dimethylnitrosamine itself may be toxic and react with some important cell constituent. It may be metabolized to produce a toxic breakdown product. Or its metabolism and breakdown may require some additional factor which, when withdrawn for this purpose, leaves the cells of the liver irreparably injured.

The experimental observations indicate that D.M.N. can produce severe liver injury in a variety of experimental animals. This makes it difficult to exclude a direct causal connexion between the handling of D.M.N. and the development of cirrhosis of the liver in two out of the three men who did so.

As a solvent D.M.N. is obviously toxic, and, from the limited experience of its use, it is clearly a dangerous one to handle despite its low volatility and consequent comparative freedom from hazards from its vapour. The absence of a strong smell or other irritant properties means that contamination of the skin and clothes may have passed unnoticed. Though it does not readily penetrate the skin of rats, it may more easily be absorbed if clothing is soaked and applied to the skin. Nevertheless there are no observations which suggest that such was the route by which the two men absorbed D.M.N. in doses sufficient to produce cirrhosis of the liver. If one assumes that man is no less sensitive than the rat, then a daily dose of 260 mg. for a man weighing 70 kg. would be the equivalent dose to that depressing

the growth of the rats on 50 p.p.m. in their diet. Twice such a daily dose would obviously be very dangerous. With an air intake of 5 litres per min. for seven hours a day a very dangerous level in the atmosphere would be 250 mg./cu.m. A safe atmospheric concentration would clearly have to be very much less, certainly not more than 25 mg./cu.m.

Summary

Dimethylnitrosamine (D.M.N.) is a potentially useful solvent on which little toxicity data have yet been presented.

Prompted by the occurrence of two cases of liver injury in men handling D.M.N., in the laboratory of a large firm, a study of its action on experimental animals was undertaken.

In rats, rabbits, mice, guinea-pigs, and dogs D.M.N. in doses of 20 to 40 mg./kg. produces a severe liver necrosis ending fatally. Other organs are not damaged.

The lesions have some features in common with those produced by carbon tetrachloride but also some distinctive features.

In dogs, rats, and guinea-pigs a striking feature is haemorrhage into the gut and peritoneal cavity.

The features of intoxication are briefly discussed.

We wish to thank the medical officer of the firm concerned for his help and interest and for arranging for supplies of pure material. We are also very grateful to Professor G. R. Cameron, F.R.S., for his advice and help on the histological material. R. F. Legge provided valuable technical assistance.

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A REPORT ON 235 CASES OF ERYSIPELOID IN ABERDEEN

BY

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For some time it had been thought locally that the incidence of erysipeloid of Rosenbach among fish workers was much higher in Aberdeen than elsewhere. For this reason we began a systematic study of the disorder, and our findings over the period June 1, 1952, to September 30, 1953, are presented in this paper.

Doctors generally are not familiar with the lesion known as erysipeloid. Because of its strong occupational association it is well known in localities where there is a risk of infection and, at least in Aberdeen, the skin picture is so easily recognized that fish workers sometimes make their own correct diagnosis of "fish hand" or "fish poisoning". Price and Bennett (1951) reporting on 51 cases, stated that "casualty officers working near meat and fish markets, slaughter-houses, and hotel districts, are quite familiar with the disease and regard it as being by no means uncommon".

Because the clinical picture has been adequately described by many authors only a brief description is given here. The infection first appears as a reddish-blue swelling on the finger or hand, varying in size from 1 to 10 sq. cm.; the edge is raised, well demarcated, and slowly advances. The patient feels a burning, itching pain at the site and often there is a sensation of tightness in the inflamed area. Some stiffness and slight pain are common in the interphalangeal joints near the lesion.

In almost all cases the occupation of the patient is a useful guide to diagnosis. The infecting organism is a strain of *Erysipelothrix rhusiopathiae*, the causal organism of swine erysipelas, and though the natural history of erysipelothrix is uncertain, it is widely distributed in nature. The source of infection in man is invariably animal or vegetable matter, and the occupations commonly associated are those in which contact with fish, meat, or poultry is entailed; thus fish workers, slaughtermen, butchers, cooks, and housewives have been the commonest reported sufferers (Klauder, 1938; King, 1946; Price and Bennett, 1951). In a very high proportion of patients there is a history of injury—a prick from fish scale or bone, a knife cut or other minor breach of the skin—followed a few days later by the typical appearance of the infection. After one to three weeks the lesion disappears spontaneously. It is essentially a localized infection, general symptoms being unusual and complications rare. Suppuration does not occur and surgical interference is unnecessary.

Diagnostic biopsy has been performed, but Price and Bennett (1951) found that the proportion of positive cultures was not high enough to make the procedure of great value in diagnosis. We agree with Goodwin (1950) that "In view of the ease in diagnosing the condition clinically, biopsy of the lesion is not justifiable".

A striking feature of erysipeloid is its seasonal incidence. Numerous writers have noted the increased frequency of cases in summer and early autumn and its virtual disappearance in winter and spring.

The Aberdeen Cases

The casualty department of Aberdeen Royal Infirmary is situated in the city centre about one mile from the harbour where fish are landed; near the market lie about 200 separate "fish houses" where the fresh fish are prepared for sale by various processes. About 2,500 workers are employed in market and fish premises; the proximity of the casualty department to the industry has for many years made it convenient for fish workers to attend there for treatment of hand injuries and infections. Our 235 cases were all observed in the casualty department by one of us (D. M. P.) who is familiar with the condition, and though biopsy has not been performed we are confident that only genuine cases have been included in the study.

Between June 1 and December 31, 1952, 71 cases were observed; we cannot be certain that all cases of erysipeloid attending casualty in 1952 were

recorded since it took some time to ensure that every patient with the disease was referred to the senior casualty officer. From January 1 to September 30, 1953, 164 cases were observed ; this higher incidence is at least in part due to better methods of detection and we are convinced that it is a true indication of the frequency of the disease as seen in the casualty department.

Clinical Features

Seasonal Incidence.—Table 1 shows the monthly distribution of the 235 cases.

TABLE 1
NO. OF CASES IN EACH MONTH FROM JUNE, 1952, TO SEPTEMBER, 1953

Month		J	F	M	A	M	J	J	A	S	O	N	D	Totals
No. of cases	1952						4	20	18	13	6	6	4	71
	1953	0	0	1	0	1	9	84	42	27				164

The expected seasonal variation is well revealed but we have carried the study of this association a step further. The Meteorological Office at Dyce Airport on the outskirts of the city provided us with hourly air temperature readings (dry bulb) from which we computed mean weekly temperatures for the relevant periods in 1952 and 1953 ; the association between temperature and the incidence of erysipeloid is shown in Table 2 and Fig. 1.

There is a significant correlation between the two variables ; it appears that in some way the two are connected but we wish to emphasize that the data do not reveal the nature of the relationship.

Occupational Factors.—Table 3 sets out the occupational distribution of the 235 cases.

Two hundred and twenty-six (96%) of our cases were in some way connected with the fish trade. We are aware that patients in other occupations where erysipeloid is uncommon would probably be seen by their family doctor and therefore our series must have some occupational bias towards fish workers. But their preponderance in Table 3 is so striking that even without a measure of the numbers exposed to risk of infection we feel it safe to conclude that, in Aberdeen, fish workers are the commonest sufferers.

Fish processers are in frequent and intimate contact with fish ; these are the people who actually handle the fish whereas porters and lorry drivers

TABLE 2
FREQUENCY DISTRIBUTION OF WEEKLY CASE INCIDENCE BY MEAN WEEKLY TEMPERATURE

Mean Weekly Temperature (°F.)	Number of Weeks with Number of Cases in Each Week [( ) = one week]	Mean Weekly Incidence ($\frac{\text{No. of Cases}}{\text{No. of Weeks}}$)
34·4 and below	(0) (0) (0)	0
34·5–	(1) (1) (2)	1·33
36·5–	(1) (0) (0) (0)	·25
38·5–	(1) (0) (0) (0) (0) (0)	·17
40·5–	(4) (0) (1) (0) (0)	1·0
42·5–	(2) (0) (0)	·67
44·5–	(5) (2) (0) (0) (0) (0)	1·17
46·5–	(3) (2) (2) (0) (0)	1·40
48·5–	(1) (0) (2) (1) (0) (0) (2)	·86
50·5–	(0) (0)	0
52·5–	(1) (10) (0)	3·67
54·5–	(5) (6) (7) (7) (14) (14) (24) (18) (5) (5)	10·50
56·5–	(1) (2) (6) (1) (3) (3) (4) (14) (9) (9) (12)	5·82
58·5 and over	(3) (19)	11·0

Correlation coefficients : 1952 r = 0·48 S.E. = 0·14 P < 0·01 ; 1953 r = 0·67 S.E. = 0·09 P < 0·001

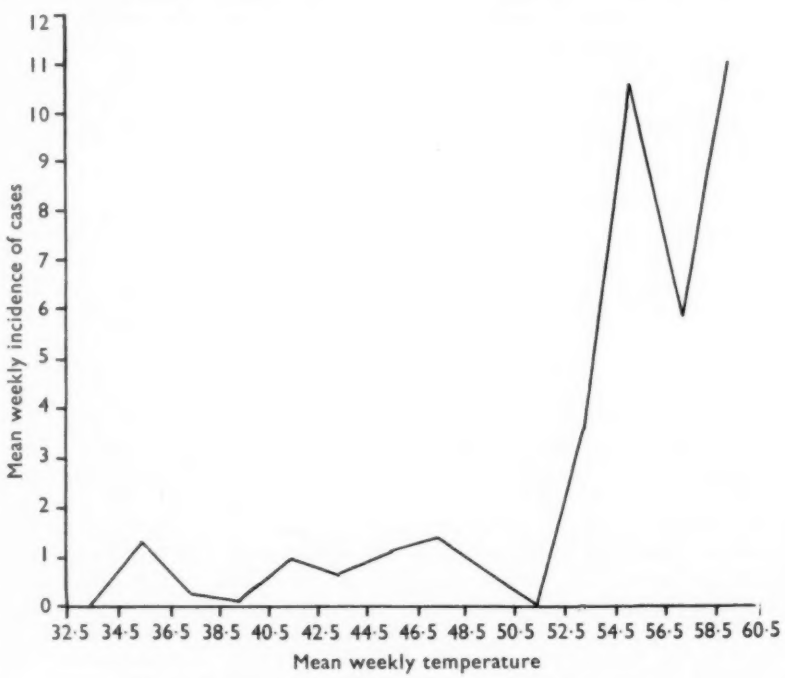

FIG. 1.—Association of temperature with erysipeloid case frequency.

TABLE 3
OCCUPATIONAL DISTRIBUTION OF CASES

Occupation	No. of Cases
Fish processers	152
Fish porters	29
Fish-lorry drivers	10
Fish-box repairers	12
Fish-meal workers	12
Fishmongers	4
Salmon overseer	1
Trawlermen	2
Fish-office clerk	1
Fish-lorry mechanic	1
Labourers	2
Total in fish trade	226
Butchers	4
Housewife	1
Car polisher	1
Pig slaughterer	1
Bus cleaner	1
Poultry cleaner	1

mainly handle boxes of fish. Fish boxes, whether full or empty, appeared to be a common source of infection and we have obtained strong evidence of this in several cases where the only known recent exposure to infection was through a fish box. For example, the car polisher who worked near the fish market had, on one occasion only, assisted a lorry driver to hoist two closed boxes of fish on to his vehicle and three days later developed a typical lesion at the site of contact. The source of infection was less certain in the mechanic who maintained fish lorries to which slime often adheres and in the man who cleaned the interior of buses used by fish workers on their way to and from work.

In every one of the 235 cases there was either a probable or a possible source of infection associated with the individual's work and it is therefore correct to label erysipeloid an occupational disease.

The Role of Trauma.—One hundred and seventy-eight patients (75%) had sustained an injury a few days before the lesion appeared. A further 20 (9%) were of the opinion that minor trauma was responsible but could not state definitely when it had been received. Fish workers are constantly receiving small wounds of the skin from fins, teeth, knives, and machines or from rough parts of fish boxes, and it is therefore not surprising that some patients could not recall precisely when they were injured.

The site of the infection is of interest in relation to the areas of skin especially exposed to risk of injury. Sixty per cent. of the lesions were found on the left hand and the most frequent sites were on a band stretching across the palmar aspect of the middle phalanx of the fingers to an area on the thenar eminence ; these are the parts of the hand in most frequent and close contact with the fish as it is held in the left hand for treatment with the knife held in the right ; thus fish processers are more liable to injure the left hand and this we believe to be the explanation of the significantly greater incidence on that hand.

Incubation Period.—This has been estimated from the 160 case histories in which the dates of specific trauma and onset of symptoms were known. Table 4 shows the frequency distribution.

TABLE 4
ESTIMATED INCUBATION PERIOD

Incubation Period (No. of Days)	No. of Cases
1–3	106
4–7	39
8–14	8
15+	7

In two-thirds of these cases an incubation period of less than four days was recorded ; in a few patients the appearance of the lesion seemed to have been delayed for one to three weeks after the injury blamed but it is quite feasible that infection entered through a later but unobserved breach of the skin. Our material certainly suggests that the incubation period is usually very brief.

General Symptoms.—Slight malaise was not uncommon but pronounced general symptoms were absent. In 39 cases (16%) lymphangitis and or axillary lymphadenitis were detected, a rather higher incidence than that reported by King (1946) but not unexpected in view of the experience of Klauder, Righter, and Harkins (1926) who found that these features were commonly associated with erysipeloid among certain fish handlers in New Jersey.

Local Signs and Effects.—The skin lesion of erysipeloid is remarkably constant in appearance and progression. It begins with sensations of heat, itch, or burning and later becomes painful, the pain being of a " prickly " character and accompanied by tenderness and tightness in the affected area. At first the skin shows a pink blush which rapidly changes through red to reddish-blue ; this violaceous tint is highly characteristic (Figs. 2 and 3). As the lesion develops the periphery spreads and shows a marked tendency to affect other digits. Slight pain and stiffness in the adjacent finger joints are common and there is a notable absence of purulence. But it should be noted that a pyogenic infection may coincide as it did in two of our cases. The infection spreads for a few days, the advancing edge being slightly raised, whilst the centre fades and slight desquamation appears.

FIGS. 2 and 3.—Erysipeloid of Rosenbach following a cut on a fish box.

In our series all the lesions were on the hand and occasionally two separate patches were seen, especially on the fingers. We have tried to estimate the duration of the lesion by noting the time taken for complete disappearance ; our data are necessarily incomplete because many patients discharged themselves, but the average duration of attendance was seven days with a range from two to 27 days. A few lesions were resistant to treatment, tending to relapse once or even twice despite daily attention and in these patients the disability was correspondingly greater. It is important to stress that, though the local disability is usually slight, a bandaged finger can be a real handicap in an occupation requiring much dexterity, and since so much of the work has to be done in moisture, we have often found it necessary to advise the patient to go off work unless a dry alternative job could be obtained. In this regard the disorder is a disabling one and of considerable socio-economic importance. Twenty-three per cent. of our patients admitted a previous attack thus suggesting that immunity following one attack is of a low order.

Treatment.—There has been some controversy about the best method of treating erysipeloid. We have made no attempt to assess statistically the therapeutic value of any remedy ; the infection is self-limiting and without a carefully planned and executed clinical trial our views are no advance on those already published. For many years it has been the routine practice in Aberdeen to dress the lesion with 10% ichthyol in glycerine but since penicillin became generally available an increasing number of patients have received it by intramuscular injection.

The findings of Barber, Nellen, and Zoob (1946) and of Sneath, Abbott, and Cunliffe (1951) suggest that penicillin should be an effective therapeutic agent in erysipeloid ; Price and Bennett (1951), though unable to draw definite conclusions from their small series, appeared to obtain favourable responses to parenteral penicillin. It is certainly our impression that penicillin is a useful addition to the usual local treatment but on this point we hope in future to produce more precise evidence.

Discussion

Our main purpose in presenting this paper is twofold. First we wish to draw attention to an infection which though common is unfamiliar to many doctors ; because of its occupational and therefore local associations the medical student may never see it and may misdiagnose it in his later practice. In Aberdeen the lesion is common and well

known but elsewhere its incidence may be sporadic, its connexion with work missed, and the sufferer denied his right to injury benefit.

Secondly we have attempted to throw some light on its aetiology. The natural history of *Erysipelothrix rhusiopathiae* is obscure but our data strongly suggest that its biological activity is in some way related to atmospheric temperature ; the disease in man virtually disappears in the colder months of the year and a warm spell is usually followed by a sharp rise in incidence. We have not been able to compute a rate per 1,000 fish workers because it is not known accurately how many people in different occupational groups are exposed to risk, but we believe that even allowing for the fluctuations in labour force there is no reasonable doubt that the correlation with temperature is a real one.

One of our colleagues, Dr. Stuart of Aberdeen University Department of Bacteriology, is studying the biology of the erysipelothrix and we are authorized to state that she has been unable to demonstrate the organism in sea-fresh fish landed and preserved under aseptic conditions ; once fish caught in the normal way have reached the market the organism is isolated with ease during the " erysipeloid season ". Our own observations on the role of contact with fish boxes suggest that fish slime and scales may harbour infection, an opinion that has been expressed by Klauder and others (1926). This author and his associates reported " about 1,000 " cases of erysipeloid among commercial fishermen on the eastern seaboard of America and concluded that among such men the disease took a more severe form ; in a further paper (Klauder, 1938) on erysipeloid as an occupational disease, it is stated that " in our studies infection was more severe when contracted from a fish source ". Klauder observed that the infection was less frequent and milder among wholesale and retail handlers of fish in markets and certainly we have in our series encountered no examples of the more severe type described by him.

During our investigation we were aware that trawlermen who might be infected with erysipelothrix would not attend the casualty department ; for 50 years the men of trawlers based in Aberdeen have had their own clinic down in the harbour area. This clinic is owned and managed by the men themselves and exists to treat and compensate (by contributory insurance) injuries received while at sea ; through the kind cooperation of Dr. John Leiper and Sister W. D. Clark, medical officer and nurse at the clinic, we have been notified of five definite cases of erysipeloid among trawlermen in the period January-October, 1953. The number of men exposed to risk is about 2,200 and we can therefore state with confidence that the incidence among trawlermen is far lower than among fish workers on land ; yet aboard ship on the way to port the trawler crews gut the fish before packing them in ice and would, it seems, be exposed to intimate risk of infection. This finding is of interest in view of the above observations by our colleague Dr. Stuart.

Further elucidation of the aetiology of human erysipeloid depends on epidemiological studies. In particular it is desirable that sources of infection should be accurately traced, for until these are defined, preventive measures must remain uncertain. If the opinion expressed in our introduction, that the infection is more common relatively in Aberdeen, is correct, data from other fishing ports might contribute towards an understanding of this minor but by no means unimportant condition.

Summary

A series of 235 cases of erysipeloid of Rosenbach is reported. There is a significant correlation between incidence of the disorder and atmospheric temperature.

In Aberdeen fish workers are the commonest sufferers.

The role of injury is discussed and it is shown clinically that fish boxes may harbour infection.

The amount of disability caused makes erysipeloid a condition of socio-economic importance and one which merits intensive epidemiological study.

We are indebted to the Meteorological Officer at Dyce Airport for the temperature readings, to Dr. F. H. C. Marriott for statistical assistance, and to Dr. Stuart, our colleague in bacteriology, for her interest and information. The colour photographs were taken by Mr. R. G. Drummond of the University photographic department. We gladly acknowledge the help given by the staff of the casualty department of Aberdeen Royal Infirmary.

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RAYNAUD'S PHENOMENON IN WORKERS WITH VIBRATORY TOOLS

BY

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The relationship between the prolonged use of pneumatic powered tools and the development of Raynaud's phenomenon was first described by Loriga (1911), and subsequently by Hunter, McLaughlin, and Perry (1945), and by Lindqvist and Flemberg (1945). This association with high frequency vibratory tools was later extended to other industrial processes. Telford, McCann, and MacCormack (1945) and Agate (1949) described " outbreaks " in workers using flex-driven (Morris-drive) rotary polishing tools, Middleton (1931) in workers on " pounding " machines in the boot and shoe industry, Gurdjian and Walker (1945) in those using light riveting hammers in aircraft construction, and Agate, Druett, and Tombleson (1946) in " hand-grinders " holding iron castings against revolving grinding wheels. Details of industrial techniques and the frequency and wave form of transmitted vibrations have been excellently reviewed by Agate and Druett (1947).

The object of the present investigation was to determine whether sufferers from vibratory tool Raynaud's phenomenon can be distinguished by any objective criteria from normal subjects or from those who develop this condition from some other cause (Jepson, 1951). Its natural history was considered particularly in relation to the occurrence of nutritional or organic arterial lesions in the digits. An attempt was also made to evaluate the amount of disability which it causes, not only at work but also in leisure hours.

Selection of Patients

Responsibility for the selection of patients was left with the Department of Occupational Health of Manchester University. Names were secured from trade unions, an independent medical officer, and the Ministry of Pensions and National Insurance. A questionnaire was sent to each patient. From information given men were selected for examination in Manchester and Birmingham. Selection took into consideration the following: (1) Representation of as many operations involving vibration as possible; (2) proximity to the examining centre; and (3) where many cases were notified from one industry the more severe were selected. This paper deals with those patients seen in the Manchester centre.

Thirteen trade unions submitted the names of 290 persons thought by their general or local secretaries to be suffering from the condition. Thirty-four men notified in this way were examined.

An industrial medical officer submitted details of 38 men working full time at clinching and flanging motor car doors. Five of the more severe cases were examined in the factory medical department.

The Ministry of Pensions and National Insurance submitted, with the patients' approval, the names of those certified as unfit for work by reason of " Raynaud's disease " or Raynaud's phenomenon. Answers to the questionnaire showed that only two patients were likely to be exposed to vibration. These two cases were included in the group. The total seen was 41, 39 of whom were at work.

Methods

Patients were seen, singly by appointment, and examined during a period of two to three hours in a private office. Following an industrial and medical history a physical examination was performed with particular emphasis on the cardiovascular and musculo-skeletal systems. A haemoglobin estimation, urine examination, estimation of the erythrocyte sedimentation rate, and a radiological study of the hand, which included in every exposure the same reference metacarpal bone, allowing valid comparisons to detect minor degrees of bony rarefaction. An attempt was made to produce " white

fingers", characteristic of Raynaud's phenomenon, by immersing the hand in cold water, and in addition a more detailed investigation of the behaviour and structure of the digital vessels was made by applying the reactive hyperaemia and heat-flow disc tests.

Clinical and Occupational History

Seven of the patients in the series were suffering from conditions not directly related to their occupation and are therefore excluded from the following analysis. The ages of the remaining 34 patients (all males) ranged from 26 to 57 years (mean, 42 years). Details of trades, ages, the interval between the start of work with the vibratory tool and the onset of the patient's complaint, and the total duration of the causative work will be found in Table 1.

TABLE 1

SUMMARY OF OCCUPATIONS AND HISTORIES OF 34 PATIENTS WITH RAYNAUD'S PHENOMENON

Occupation	Age	Years of Work with Vibrating Tools		No. of Digits Involved
		Total	Before Onset of Symptoms	
Pneumatic drilling in limestone, granite, or gypsum (6 patients)	42	13	8	3
	42	25	4	4
	43	12	4	3
	44	24	4	10
	49	20	17	8
	54	15	1½	10
Shoe pounding (4 patients)	26	5	2 months	10
	31	12	1	9
	33	5	9 months	10
	41	12	4	8
Pneumatic chiselling in iron, steel, phosphor-bronze (8 patients)	31	5	1½	8
	35	7	1½	8
	36	12	10	7
	37	16	4	4
	38	17	10	3
	50	27	14	3
	52	23	19	2
	53	14	3	8
Pneumatic riveting (2 patients)	45	7	1	8
	53	26	20	8
Flex-driven grinding in steel, iron (4 patients)	41	4	1	1
	53	20	9	9
	53	6	3	10
	57	5	4 months	2
Hand grinding in carborundum, steel (4 patients)	39	5	2	5
	45	30	27	6
	46	7	1½	8
	47	4	3	8
Pneumatic clinching and flanging (5 patients)	27	1	4 months	3
	32	4	6 "	7
	32	7	1 month	4
	40	14	1½	3
	46	20	2	5
Wire straightening (1 patient)	31	5	2½	7

The onset of Raynaud's phenomenon followed a symptomless period of work with the vibratory tool which ranged from one month to 20 years. The workmen affected in any particular trade seldom included all of those handling pneumatic tools, and the duration of work before the onset of symptoms varied from man to man. Thus, among the group of 10 workers using pneumatic chisels and riveters, two patients first noticed "white fingers" within 18 months of beginning work, while for another two the interval was 19 and 20 years respectively. The period of time before onset did not appear related to a family or previous personal history of Raynaud's phenomenon, the degree of exposure to cold at work, age, or anatomical type of fingers. Patients in some trades, such as flangers and clinchers in the motor industry and shoe pounders, were particularly liable to develop it. A survey of 38 full-time clinchers, 100% of those thus employed at one factory (five of whom are included in the present series), showed that four had no symptoms, 23 developed symptoms within one year, five within two years, four within three years, and two in a period at work of more than three years. By contrast, five of the six limestone and gypsum workers interviewed noticed the onset after a period of four to 17 years' drilling.

It is common to all of the trades examined in this review for the onset to be earlier and for the condition to be more severe in fingers to which most vibration is transmitted. For example (in right-handed workers) the flex-driven grinding machine is gripped and guided near the grinding end by the little, ring, and middle fingers of the left hand. It was in these fingers that Raynaud's phenomenon inevitably first developed. In the pounding process employed in the boot and shoe industry the sole is held by both hands equally, being gripped most firmly by the thumbs and forefingers as it is pressed against the pounding roller. These workers develop Raynaud's phenomenon simultaneously and symmetrically in the thumbs and forefingers of both hands. The fingers less directly involved by the vibratory stimuli are affected much later on.

The severity of attacks of "white fingers", that is the facility with which they are induced and their persistence, appears to reach a maximum some years after their onset and thereafter further exposure does not appreciably increase the severity. Thus T. H., a shoe pounder, developed symptoms within one year of starting this work. Attacks became more frequent and prolonged over the next two to three years and then remained unchanged for the following nine years of similar employment.

Thirteen patients had abandoned the causative trade from one to nine years (mean, four years) before interview; three because of Raynaud's

phenomenon, seven because of redundancy, and three by promotion. With one exception, they stated that attacks persisted unchanged or became more severe and frequent after their change of employment. One patient who worked as a clincher for four years developed symptoms only after he had ceased to use the pneumatic tool.

Patients complained that attacks of white " dead " fingers were most noticeable in the winter months, in early mornings on rising, and during outdoor activities such as going to football matches, fishing, or gardening. Washing the hands in cold water was frequently said to be a precipitating cause. Relief was obtained by warming affected fingers in hot water, by friction or radiant heat. Attacks in the initial stages of the disorder involved only the terminal segment of a finger. Later the whole digit became blanched to the metacarpo-phalangeal joint and additional fingers were affected. The " white " phase was accompanied by cold ache and numbness. Relaxation of the digital vessels was followed by periods of digital cyanosis and the pinkness and paraesthesiae of reactive hyperaemia.

Hands recovered completely between attacks and were of normal colour and warmth, in contrast to the usual high peripheral tone or cyanosis seen in other cases of Raynaud's phenomenon. None of the patients complained of nutritional lesions in digits such as soft tissue wasting, ulcers, or gangrene.

Raynaud's phenomenon rarely interfered to a marked degree with the patient's work. This was particularly true of those working indoors in a warm atmosphere as both body and finger temperatures were higher than that required to precipitate an attack. In outdoor workers, for example limestone drillers, numbness, clumsiness, and an ache in the fingers during cold winter months compelled them to seek frequent relief from a neighbouring brazier. The mean period of work in causative trades for the 34 patients following the onset of symptoms was seven years (range one to 21 years). Loss of time or earnings was not a frequent or dominant complaint. All patients, however, complained of considerable handicap during their leisure hours in as much as their pleasure in gardening, swimming, and watching or playing outdoor games was impaired by numb or painful fingers.

Seven patients (excluded from the 34 patients reviewed above) claimed to be totally incapacitated by this condition. These patients (six men and one woman) were without exception suffering from other conditions which could not properly be attributed to their occupations, namely, generalized atherosclerosis (two), acrosclerosis (one), rheumatoid arthritis (one), athetosis (one), writer's cramp (one). One patient was thought to be a malingerer.

Physical Examinations

None of the 34 patients was found to have any neurological or connective tissue disease but two had a mild hypertension. The peripheral limb pulses were present and of good volume. *X*-ray examination of wrists and hands demonstrated carpal or metacarpal cysts in four patients although in none were symptoms referred to the carpal region. Haemoglobin, erythrocyte sedimentation rate, and urinary examinations were normal.

Accessory Tests.—These tests were designed to determine whether the lumina of the digital arteries were normally patent in the intervals between vasospastic attacks and whether an abnormal reaction by the digital vessels to finger cooling could be demonstrated objectively. The lightly clothed patient was rested before examination for 45 to 60 minutes in a constant temperature room (21° C.).

Reactive Hyperaemia Test.—This was used to exclude gross organic occlusion in the digital arteries (Pickering, 1933).

The hands were immersed to the wrist in a water bath at 40° C. for five minutes; arterial occlusion was maintained by means of a sphygmomanometer cuff on the upper arm. At the end of this time the hands were removed from the water and on releasing the cuff a pink flush spreading symmetrically to the tips of the digits within four seconds was taken to be evidence that the lumina of the digital arteries were normally patent. All of the 34 patients were found to be normal by this criterion.

Precipitation of Raynaud's Phenomenon by Hand Cooling.—The hands were immersed in a stirred water bath at 15° C. for 15 minutes; during the first five minutes the circulation was occluded with a sphygmomanometer cuff on the upper arm to ensure rapid cooling of the digits. Fourteen of the 34 patients tested developed white " dead " fingers, typical of Raynaud's phenomenon, in one or more digits. Many of the remaining 20 developed a varying degree of cyanosis in the digits, the significance of which could not be evaluated (Table 2).

TABLE 2
EFFECT OF HAND COOLING IN 34 PATIENTS

Age (years)	No. of Subjects	Precipitation of " White Finger "	Absence of " White Finger " ± Cyanosis
20–39	13	6	7
40–59	21	8	13

Heat-flow Test.—This test was designed to estimate the reactions of the digital and skin blood vessels to cold by measuring the heat-flow (in calories per square centimetre of skin per minute) from the skin covering the pulp space of an affected finger by means of a copper-tellurium heat-flow disc (Hatfield, 1950; Catchpole and Jepson, 1954). The disc was attached to the finger with cellulose tape and the whole hand immersed in continuously stirred water of 15° C. while the circulation was occluded by a sphygmomanometer cuff on the upper arm. The heat loss from the finger to the water was recorded by a spot galvanometer (450 ohms). At the end of five minutes' immersion the heat exchange between the finger skin and the water had virtually ceased (galvanometer reading less than 10 divs.). The cuff was then removed, the hand remaining immersed in the water bath for a further 10 minutes. If the digital arteries reacted to the cooling by spasm then no blood could pass into the fingers on release of the cuff and the heat flow between the skin and the water approximated to zero (negative test). Alternatively if the vessels responded to the vasodilator stimulus of arterial occlusion (Lewis and Grant, 1925) then relaxation occurred and a varying degree of increase of heat flow from the finger to the water bath was detected (positive test).

Twenty-four patients and 29 normal controls were investigated by the heat flow disc test (Table 3).

TABLE 3

RESULTS OF HEAT-FLOW DISC TEST IN PATIENTS WITH VIBRATORY TOOL RAYNAUD'S PHENOMENON AND NORMAL CONTROLS

Age	Patients		Normal Controls	
	No.	Negative Result*	No.	Negative Result
20–39	11	7	17	1
40–59	13	6	12	7
Total	24	13	29	8

*Negative result means here persistent spasm.

Thirteen patients and eight controls gave a negative test indicative of vascular spasm. In the remainder of both patients and controls the test was positive. Among the 24 patients visible "white fingers" were demonstrated by the cooling test in nine and a "white finger" was constantly accompanied by a negative heat-flow test. The significance of the test and the findings in normal and abnormal cases are discussed in detail elsewhere (Jepson, 1954).

Discussion

There can be no doubt that long-continued use of a certain type of vibratory tool eventually leads to Raynaud's phenomenon in the fingers. Comparative figures are not available of the incidence of this condition in different trades, but in many its onset is early and its incidence high. Thirty-two of 37 hand grinders developed it within 21 months (Agate and others, 1946); 184 of 278 workers scrufing and polishing metal castings with rotary hand tools were affected (Agate, 1949). As recorded above, 23 out of 38 clinchers and flangers developed it within one year of starting this type of work.

The physical conditions which bring about the change of behaviour in the digital arteries are partially defined. Agate and Druett (1947) by using a piezo-crystal recording technique suggested that critical frequencies leading to Raynaud's phenomenon were about 40 to 125 cycles per second. Many other variables may be of equal or greater importance such as amplitude and wave form of fundamental and secondary harmonics, strength of grip required, type of material on which work is performed, the operator's skill, the mechanical efficiency and mass of the tool, and each individual's susceptibility to the condition.

The pathological lesion which the high frequency physical trauma produces is unknown. Histological studies have not, as far as is known, been made, since amputation of affected digits is not required. The absence of nutritional lesions in the vibratory tool form of Raynaud's phenomenon suggests that the abnormality is confined to the muscle of the media and does not include endothelial proliferation with encroachment upon the lumen. The malady appears to be limited to a behavioural change on the part of the digital vessels in response to cooling, and long-continued work with causative tools does not lead to the onset of narrowing or blockage of the digital artery. This conclusion was also reached clinically by Hunt (1936), Lindqvist and Flemberg (1945), Telford and others (1945), and Agate (1949), and is confirmed in the present study by the lack of nutritional lesions and the normal reactive hyperaemia tests. Arteriography in many similar patients has previously demonstrated normal vessel patterns (Jepson, 1951). It is emphasized that the group of seven patients who claimed to be incapacitated by Raynaud's phenomenon were in fact suffering from general systemic diseases totally unconnected with the use of vibratory tools. It is evident that certain tools may indeed cause other and more severely disabling traumatic lesions but these differ in nature and possibly in precise cause from Raynaud's

phenomenon. For example, the group of five clinchers and flangers examined in this series all showed evidence of digital nerve lesions, joint pain and swelling, and cramp or weakness in the long flexor muscles. Dart (1946) and Peters (1946) have reported similar symptoms in men using air-turbine driven grinding tools. Agate and Druett (1947) suggested that frequencies above 160 cycles per second may cause this latter clinical picture.

It is apparent that the vascular tests used to confirm the presence of Raynaud's phenomenon have proved disappointing. In many instances cooling fails to provoke visible evidence of spasm of the digital artery in patients who are undoubtedly suffering from attacks of Raynaud's phenomenon. Such patients seem to need supplementary stimulus of vasoconstrictor activity from body cooling before the digital colour change can be produced. Although the proportion of confirmatory results is slightly higher with the heat-flow disc test than with the visual test, the issue is further complicated by the frequency with which a control sample of normal adults, especially in the older age groups, give a negative heat-flow test indicative of vascular spasm (Jepson, 1954). Nor does the objective confirmation of vascular spasm allow a diagnosis to be made of Raynaud's phenomenon due to the use of a vibratory tool. Its onset in adult life secondary to an underlying disease process is most commonly due to atherosclerosis, thromboangiitis obliterans, or a form of rheumatoid arthritis. Attacks of "white fingers" seen in workers with vibratory tools do not in themselves differ essentially from many attacks due to other causes. There are, however, some associated features which are characteristic of this condition when it is due to the use of vibratory tools and assist in the diagnosis; the onset is related to a particular type of work involving the transmission to the hands of high frequency vibrations; there is an earlier and more severe form in fingers to which most vibration is transmitted, and it is therefore usually asymmetrical in development but can sometimes be equally distributed in both hands as in the shoe-pounder. The lumina of the digital arteries are not occluded and there are no nutritional lesions in the fingers. Primary arterial disease and rheumatoid arthritis are absent.

The degree of disability varies considerably because of variations in the severity of Raynaud's phenomenon and by reason of the man's type of work and hobbies. It is evident that among those working in heated buildings time or wages are seldom lost. In those working out of doors, particularly limestone drillers, much time may be spent warming the hands at a neighbouring fire. Considerable discomfort may be experienced from cold-ache associated with "white fingers". Two major complaints are the handicap which the disability causes in the enjoyment of outdoor recreations and the difficulties involved when the patient changes his job to one necessitating fine finger control. In such circumstances there may be considerable disability and one which, as far as can be ascertained, is unlikely to improve with the passage of time.

Summary

Forty-one patients from various trades thought to be suffering from Raynaud's phenomenon caused by vibratory tools were investigated. Seven of the patients were suffering from some other condition which could not possibly be attributed to this type of work.

In the remaining 34 patients vascular tests exclude organic occlusive lesions, and in approximately one half of the cases confirmed the liability to Raynaud's phenomenon. The value of tests was limited by false positive and negative results in patients and normal controls. The diagnosis of Raynaud's phenomenon caused by vibratory tools must therefore at present be made on clinical grounds.

The use of some forms of vibratory tool leads to a much higher incidence of Raynaud's phenomenon with earlier onset than does the use of other forms of tool. In occasional instances, nearly all the individuals exposed for one or more years are affected.

The severity of the Raynaud's phenomenon reaches a maximum within a few years of its first appearance and further exposure does not apparently change its severity.

There is little evidence to suggest that Raynaud's phenomenon, once established, will disappear or appreciably abate in severity even though the patient abstains from the causative employment.

Raynaud's phenomenon rarely interferes to a marked degree with the patient's work. It may, however, limit the enjoyment of his leisure to the extent that gardening, swimming, and the observation of or participation in outdoor games may be impaired by reason of numb or painful fingers.

I am indebted to Professor R. E. Lane and Miss N. M. Goodman, of the University Department of Occupational Health, who have undertaken all the gruelling staff work required to organize this survey, to Dr. Raynard for the details of the survey of the clinchers in the motor industry, and to Professor Boyd in whose department the investigations were carried out.

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THE TREATMENT OF COMPLICATED PNEUMOCONIOSIS WITH ISONIAZID

BY

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Work at the Pneumoconiosis Research Unit and elsewhere has shown that complicated pneumoconiosis is relatively common in the mining areas of Wales (Hart and Aslett, 1942 ; Cochrane, Davies, and Fletcher (1951), that it is severely disabling in the later stages (Gilson and Hugh-Jones, in the press) and definitely reduces the expectation of life (Stewart, Davies, Dowsett, Morrell, and Pierce, 1948). Neither change of occupation nor treatment has been shown to alter the course of the disease. On the basis, however, of the considerable evidence that tuberculosis plays a major part in the aetiology of the progressive massive fibrosis (P.M.F.) of complicated pneumoconiosis (Fletcher and Gough, 1950 ; Van Mechelen, 1935) it seemed reasonable to see whether the rate of radiological progression could be influenced by chemotherapy which was known to be effective in the treatment of pulmonary tuberculosis.

A therapeutic trial of this kind presents unusual difficulties. To allow the maximum chance of success it was decided to include only the earlier cases of progressive massive fibrosis, occurring in relatively young men. However, men in this group have few serious symptoms and are in many cases earning high wages in the coal industry. It would therefore not have been justifiable to keep a large number of them in hospital for prolonged treatment unless very encouraging results of a pilot trial on in-patients had been available. On the other hand, a field experiment of streptomycin involving regular injections would have led inevitably to a high lapse rate. We finally decided therefore on a controlled trial using isoniazid. This avoided the administrative difficulties of injections and the toxic side-effects of streptomycin and P.A.S. which might have been serious in working men. As we were going to treat only cases in which the sputum was negative for tuberculosis, it seemed reasonable at the time the trial started, which was immediately isoniazid became available in this country, to proceed without waiting for further knowledge about the risks of drug resistance. The full extent of the problem was not then known.

The Design of the Trial

The trial was designed to determine whether the administration of isoniazid to cases of early P.M.F. would diminish the radiological progression rate, which was known to be about 12·5% per annum for all cases, and greatest in early lesions in young men (Pneumoconiosis Research Unit, unpublished data). Accordingly men were selected who were thought likely to show, in the absence of treatment, the most rapid radiological progression ; they were visited at their homes, volunteers were enlisted, and subsequently divided at random into two numerically equal groups, the treated and the controls.

Treatment

The dosage scheme used by the M.R.C. Tuberculosis Chemotherapy Trials Committee was followed (Medical Research Council, 1953) ; a dose of 100 mg. of isoniazid was given twice daily for three months to half the men ; the remainder received indistinguishable inert tablets. The first three-month course was separated from a second similar course by an interval of four months. Assessment of the progress of the two groups was made five months after the end of this second course.

During each course tablets of 50 mg. each were distributed in bottles of 100, i.e. 25 days' supply, and every man or his wife was visited at least four times during each three-month course. The patient's physician was asked to continue treatment through intercurrent illnesses unless its discontinuation was thought essential.

Selection of Cases

The basic requirements for all cases before acceptance into the trial were : (1) That they should have early massive fibrosis visible on plain postero-

anterior films and on tomography. (2) That they were radiographed by this Unit within the previous two years, and at the time of radiography were under the age of 50 years. (3) That their sputum should not be positive for *M. tuberculosis*. (4) That they should have no other medical condition likely to interfere with the successful completion of the course, e.g., they should have no albuminuria, as isoniazid had been reported to have toxic effects on the kidneys.

Chest radiographs of over 95% of all miners and ex-miners in one mining valley had been taken in the Rhondda Fach Scheme (Cochrane, Cox, and Jarman, 1952), and, of the total of 6,026 films, 788 showed complicated pneumoconiosis ; 296 of these were of men under the age of 50 with early massive shadows (Categories A and B, International Classification, Fletcher, 1950). The films of these 296 were re-read and from them were excluded all cases with sharply defined shadows (an appearance thought to be associated with contraction and possibly indicative of a less active or burnt-out phase), all cases with cavitation, and all cases with the characteristic type of chest radiograph associated with rheumatoid arthritis in coal-workers (Caplan, 1953). This left a total of 173 men. The trial was explained to each of these men during a home visit, and 138 of them volunteered to participate. These men formed the group investigated before inclusion in the trial.

Preliminary and Intermediate Investigations

Before treatment was started, the following investigations were carried out : (*a*) Postero-anterior chest radiographs were obtained and at least three tomographs taken at 2 cm. intervals, routinely at 8, 10, and 12 cm., with further cuts when indicated. (*b*) Two laryngeal swabs were taken from each man. (*c*) The erythrocyte sedimentation rate was determined by the Westergren method. (*d*) The Middlebrook-Dubos agglutination test was performed (Middlebrook and Dubos, 1948 ; Scott and Smith, 1950). (*e*) Each man was weighed. (*f*) Urine specimens were tested for protein.

Urine examinations were repeated after one month's treatment, at the end of the first course, and again at the beginning and end of the second course. All men were weighed at the end of the first course and before the second course, and plain postero-anterior chest radiographs were taken again at the start of the second course of treatment. After the preliminary investigations, eight of the 138 volunteers were excluded from the trial, three for absence of confluent opacity on tomography, three for albuminuria, one for mental deficiency, and one for carcinoma of the stomach. These exclusions left 130 men in the trial ; they were divided at random into two numerically equal groups.

Exclusions during the Trial

In a field trial of this kind, where close supervision is impossible, and the majority of men have few serious symptoms, lapses are inevitable, and a number of men omitted to take tablets during holidays and intercurrent illness. Any single lapse of up to two weeks has been ignored provided treatment thereafter was taken regularly, but a number of men who stopped taking tablets regularly, or failed to complete each course within one month of its intended date of completion, have been excluded from the analysis.

The final analysis was made on 101 of the 130 volunteers, 52 of the 65 treated, and 49 of the 65 controls. The groups were compared for various characteristics none of which showed any material differences between the groups at the start of the trial, although the treated group was rather lighter in weight than the controls (means 134 and 139 lb. respectively). This difference is, however, less than its standard error. The mean ages of men in these two groups at the start of the trial were 42·1 years (range 27·5 – 51·3 years) and 42·3 years (range 29·4 – 51·1 years) respectively. Lapses were greater among the treated than among the controls during the first course, but were twice as great among the controls during the second course. However, none of the differences is greater than could be attributed to chance. The reasons for discontinuing treatment are shown in Table 1.

TABLE 1

REASONS FOR DISCONTINUING TREATMENT IN SUBJECTS EXCLUDED DURING THE TRIAL

Reasons for Discontinuation	1st Course		2nd Course	
	Treated	Controls	Treated	Controls
Positive sputum	—	—	—	1
Haemoptysis	1	—	1	1
Giddiness	1	—	1	—
Drowsiness	1	—	—	—
Nausea and epigastric pain	1	1	—	1
Intercurrent illness	1	1	1	1
Psychological	2	2	3	8
Totals	7	4	6	12

Final Investigations and Assessment

The final investigations were carried out 16 months after the preliminary investigations, and included all the tests except the E.S.R. and Middlebrook-Dubos agglutination test which were done originally only to determine whether they had any prognostic significance.

The initial and final chest radiographs were read separately by two pairs of physicians who were unaware of the treatment given to each man. Tomograms were used for confirmation when any reader considered progression to have occurred, but where the plain films showed no progression, tomograms were ignored; when doubtful progression read on plain films was not confirmed on tomography, no change was recorded; there remained a small number of cases, however, in which a final reading of doubtful progression was thought essential. There were 23 films in which there was disagreement between the two pairs of readers; these were read again in consultation and an agreed decision was reached for each film.

Results

X-ray Changes.—The *x*-ray changes between initial and final films of the two groups are shown in Table 2. The differences in the proportions progressing are not statistically significant. This Table includes one control who developed positive sputum and was thereafter excluded from the trial; a chest radiograph taken after the completion of the first course of isoniazid had also shown progression.

TABLE 2
RADIOLOGICAL CHANGES IN TREATED AND CONTROL GROUPS AT END OF TRIAL*

	Progression	? Progression	No Change	Total
Treated	8 (15%)	3 (6%)	41 (79%)	52 (100%)
Controls	10 (20%)	5 (10%)	35 (70%)	50 (100%)

Grouping "Progression" and "? Progression," $\chi^2 = 0{\cdot}636$ for 1 degree of freedom, $P = 0{\cdot}425$.
*One control subject who developed a positive sputum and was thereafter excluded has been included here as a progressor.

An attempt was made to determine in which interval the progression had taken place but this was found to be too difficult. Table 3 shows the inter-observer error in the initial readings for progression. The extent of the error is somewhat larger than was expected from our experience, based on repeated surveys at collieries, but the interval between the two radiographs was in this case shorter. It is also probably true that the use of tomographs increased the differences between observers. Yerushalmy and others (1951) investigated the inter-observer error in reading progression and regression in cases of pulmonary tuberculosis and found that it was very much larger than their measurements of error in straightforward diagnosis had led them to expect.

TABLE 3
AGREEMENT BETWEEN TWO PAIRS OF READERS ON X-RAY CHANGES AT END OF TRIAL

		Readers C and D			
		Definite Progression	? Progression	No Change	Agreement of Readers C and D with A and B
Readers A and B	Definite Progression	9	3	6	9/18 (50%)
	? Progression	1	2	3	2/6 (33%)
	No Change	6	4	67	67/77 (87%)
	Agreement of readers A and B with C and D	9/16 (56%)	2/9 (22%)	67/76 (88%)	101

Weight Changes.—Both groups increased in weight throughout the trial, the treated group by 2·7 lb. on the average, the controls by 1·8 lb. A detailed analysis of the 49 controls and 49 of the treated group, chosen at random from the full 52 to simplify the statistical analysis, showed no evidence of heterogeneous weight changes among individual men, nor of any significant difference between treated and controls. If the weight changes are expressed as a linear regression on time of weighing, this can be expressed as a gain of 0·12 lb. per month.

Other Changes.—Subjective assessment of symptoms showed no significant difference between the two groups at the completion of the trial. There were no deaths from pneumoconiosis in either group; one man in the control group had a series of melanoptyses three weeks after finishing the first course of tablets and laryngeal swabs gave positive evidence of *M. tuberculosis*.

Haemoptysis is a remarkably common symptom in complicated pneumoconiosis; seven of the 52 treated cases had at least one haemoptysis, and two others had been stopped treatment for persistent haemoptysis and are excluded from the analysis. Four of the 49 controls had a haemoptysis and one other stopped taking tablets on account of this symptom; 14 of the 130 men (11%), therefore, had at least one haemoptysis during the 16-month period.

Three of the 52 treated cases experienced melanoptysis during the period of the trial as against two of the 49 controls, but two other men in the control group had melanopytsis but are excluded from the analysis for having failed to complete treatment.

Toxic Effects.—In a report on the toxicity of isoniazid, the Committee on Therapy of the American Trudeau Society (1953) estimated toxic reactions in about 5% of adult patients treated with doses be-

tween 150 and 300 mg. daily ; these were sufficiently severe in 1% to contraindicate further treatment with the drug.

In this trial toxic effects were not frequently attributable to isoniazid ; treatment was suspended in only two cases, both for persistent haemoptysis, but in neither case was there good evidence that isoniazid was responsible. Two others developed transient albuminuria during the first course of tablets but this did not persist in either case.

Fourteen other men attributed symptoms to isoniazid tablets, including three who discontinued treatment. These symptoms were giddiness (6), disturbances of micturition (2), diarrhoea (2), drowsiness (2), headache (1), and nausea and epigastric pain (1). On the other hand seven of the controls attributed symptoms to the inert tablets as follows : giddiness (3), palpitations (2), haemoptysis (1), and epigastric pain (1).

Progression Related to Occupation.—Previous investigations by the Pneumoconiosis Research Unit had suggested that the progression of complicated pneumoconiosis was independent of dust exposure.

TABLE 4
RADIOLOGICAL CHANGE IN RELATION TO DUST EXPOSURE

Occupational Environment	Progression	? Progression	No Change	Total
Dusty 1	4 (19%)	2 (10%)	15 (71%)	21
Non-dusty 2	13 (16%)	6 (8%)	61 (76%)	80

1. In this group are included colliers, "hard-headers," repairers, packers, conveyor shifters, and hauliers.
2. In this group are included surface workers, engine drivers, and ex-miners.
Grouping "Progression" and "? Progression," $\chi^2 = 0{\cdot}029$ for 1 degree of freedom, $0{\cdot}8 < P < 0{\cdot}9$.

In Table 4, the rate of progression of those exposed to dust is compared with those not so exposed ; though the time interval is short, these findings appear to confirm the earlier work ; the differences in the proportions progressing are not statistically significant.

Middlebrook-Dubos Agglutination Test.—Only four men in the trial gave a positive result at a titre of 1 in 8, a result which, by the method used, is said to be comparable with the findings in a control group of healthy non-tuberculous people (James, personal communication). None of these four showed any radiological progression during the trial, and three of the four had erythrocyte sedimentation rates of 10 mm. in one hour or less ; furthermore the test was negative in the one case where the sputum became positive. It would seem therefore that a positive test is probably not indicative of a poor prognosis in complicated pneumoconiosis.

Erythrocyte Sedimentation Rate.—Martin (1948) found that the sedimentation rate had a definite prognostic value in complicated pneumoconiosis ; the importance of his findings is somewhat diminished by the fact that 50% of his whole group died within two years, as this means his original group was very highly selected. Our findings in Table 5 confirm and

TABLE 5
RADIOLOGICAL CHANGE IN RELATION TO E.S.R.

E.S.R. (Westergren) (mm./1 hr.)	Progression	? Progression	No Change	Total
	No.	No.	No.	No.
0–	6 (9·0%)	7 (10·4%)	54 (80·6%)	67 (100%)
10–	6 (28·6%)	0	15 (71·4%)	21 (100%)
20+	5 (38·4%)	1 (7·8%)	7 (53·8%)	13 (100%)

extend the observations by Stewart and others (1948) that the E.S.R. has some prognostic value in P.M.F. in that the proportion showing definite or ? progression increases with increasing sedimentation rate, but analysis of the results grouped as in Table 6

TABLE 6
ANALYSIS OF DATA OF TABLE 5

E.S.R. (Westergren) (mm./1 hr.)	Progression and ? Progression	No Change	Total
0–	13 (19·4%)	54 (80·6%)	67 (100%)
10+	12 (35·3%)	22 (64·7%)	34 (100%)
Total	25 (24·8%)	76 (75·2%)	101 (100%)

$\chi^2 = 2{\cdot}264 \qquad 0{\cdot}1 < P < 0{\cdot}2$

shows no statistically significant effect, and analysis of those with a raised E.S.R. (10 mm. in one hour or more) indicates (Table 7) that even amongst these cases we still have no means of altering the course of the disease, so the value of a test which tells us that one man is more likely to progress than another is rather limited.

TABLE 7
RADIOLOGICAL CHANGE IN SUBJECTS WITH RAISED E.S.R. (10 MM./1 HR. OR MORE)

	Progression	? Progression	No Change	Total
Treated	5	1	11	17
Controls ..	6	—	11	17

Discussion

The trial shows that isoniazid is not dramatically effective in treating cases of early massive fibrosis with negative sputum, but it should be stressed that it may well be of value in cases with positive sputum. No single significant difference appeared in the progress of the treated and control groups, but it is important to remember that, just as successful results may occasionally occur through the play of chance alone, so also may a real effect be obscured in one trial by a combination of chance effects. Fig. 1 represents, in respect of progression rates, what the trial can be claimed to have shown with reasonable certainty (the method used to derive this figure is given as an appendix). In this figure different progression rates in controls and treated are plotted against each other; the observed result, 21% showing definite or ? progression among the treated subjects, 30% among the controls, is plotted as a cross. The true effect of isoniazid may be asserted to be within the curved zone surrounding the cross; the boundary of this zone defines pairs of progression rates which just differ significantly (at the 5% level) from the observed pairs. If it is said, for example, that a 30% natural progression rate is reduced to 10% in the treated group, then the probability of observing the results of this trial is less than 5% (since the 30 – 10 point lies outside the curved zone) and this statement may be rejected as incorrect at the 5% significance level. However, within the curved zone, a large range of different results is possible. For instance, the line connecting all equal progression rates passes through the zone; more important, so does the line connecting all points giving twice the progression rate to the controls than to the treated. We cannot claim, for instance, that a 40% progression rate in the controls and a 20% one in the treated has been ruled out by the trial results. Only by extending the trial for longer, or by including more subjects, can the range of different but concordant results be reduced.

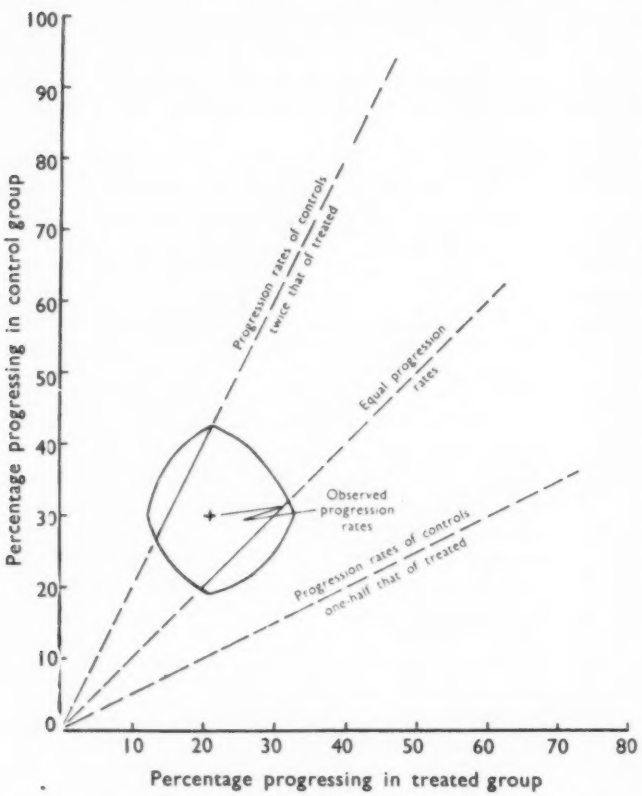

FIG. 1.—Chart showing combinations of progress rates which are compatible (probability greater than 5%) with results observed in trial.

For the present, it is perhaps reasonable to discuss the implications of the present results as if they were absolute and completely negative. It could then be argued that the lack of success of the trial was evidence against the hypothesis that tuberculosis was a factor in the aetiology of P.M.F.; when massive fibrosis becomes visible on the *x*-ray plate it is probably already a fairly fibrotic lesion, and, on the analogy with chronic fibrotic tuberculosis, we did not expect any marked radiological regression, but it is difficult to reconcile the fact that isoniazid completely failed to influence the progression of existing lesions and the development of new ones with the tuberculosis hypothesis. Similarly, if tuberculous toxicity contributed to the ill health felt by men with massive fibrosis, it might be expected that isoniazid would have caused a significant weight gain in the treated group.

A positive result with isoniazid would, we think, have been strong evidence in support of the tuberculosis hypothesis, but because the disease, if tuberculous, is a form of tuberculosis very modified by the presence of coal dust a negative result is less convincing evidence opposing it.

Summary

One hundred and thirty coal miners, all under the age of 52, with early complicated pneumoconiosis and sputum negative for tubercle bacilli, were divided randomly into " treated " and " control " groups in a trial of the effects of isoniazid in this disease.

Isoniazid, 200 mg., was given daily to the treated in two three-monthly courses at home.

The results were assessed in the 101 men who completed both courses and in one man who had developed a positive sputum at the end of 16 months. Amongst the 102 men definite or suggestive radiological progression occurred in 21% of the treated, 30% of the controls, but the difference is not statistically significant.

The trial showed no evidence that isoniazid has any dramatic effect in these cases, but the relative insensitivity of the trial did not exclude results compatible with some effect, the limits of which are discussed.

No serious complications or resistant tubercle bacilli were encountered.

We wish to record our thanks to Dr. J. C. Gilson, the Director, and our other colleagues in the Pneumoconiosis Research Unit for valuable advice and criticism, and to the Unit's field survey team who undertook much of the work involved.

Drs. J. Glyn Cox and H. M. Foreman gave helpful advice throughout the trials, and Drs. C. M. Fletcher, J. C. Gilson, and G. S. Kilpatrick kindly assisted in the reading of the films. Drs. Scott Thomson and J. Marks were responsible for the bacteriological investigations, and Drs. Geraint James and F. O'Grady carried out the Middlebrook-Dubos tests. The trial required an exceptionally high standard of radiography and this was achieved by Mr. W. G. Clarke and Mr. J. Chambers.

To all these we gratefully acknowledge our indebtedness and to the miners whose willing cooperation made the trial possible.

Isoniazid (as "rimifon") and dummy tablets were kindly supplied by Roche Products Limited.

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APPENDIX

Note on the Method Used to Derive Figure 1

If p_1 and p_2 are the *true* progression rates among the treated and control subjects respectively, the chance of obtaining 11 or more progressors among the 52 treated subjects studied is :

$$\binom{52}{11} p_1^{11}(1-p_1)^{41} + \binom{52}{12} p_1^{12}(1-p_1)^{40} + \ldots . \ldots . + p_1^{52} = I_{p_1}(11, 42)$$

where $I_x(p, q)$ is the incomplete B-function ratio :

$$\int_0^x x^{p-1}(1-x)^{q-1}\,dx \div \int_0^1 x^{p-1}(1-x)^{q-1}\,dx$$

Similarly, the chance of obtaining 11 or less progressors is $I_{1-p_1}(41, 12)$. The corresponding probabilities in the control group are $I_{p_2}(15, 36)$ and $I_{1-p_2}(35, 16)$.

The joint probability of the two independent samples or of more extreme ones can thus be written down at once in the form of products of two incomplete B-function ratios, and the limits of the values of p_1 and p_2 can be derived as those which make the product just less than 0·05. They can quickly be obtained by means of Pearson's tables (1934).

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SILICA AND COLLAGEN IN THE LUNGS OF SILICOTIC RATS TREATED WITH CORTISONE

BY

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The inhibiting effect of cortisone on proliferating connective tissue (Ragan, Howes, Plotz, Meyer, and Blunt, 1949 ; Spain, Molomut, and Haber, 1950a ; Cavallero, Sala, Amira, and Borasi, 1951) and phagocytosis (Spain and others, 1950b) led us to observe the effect of this hormone on the developing silicotic nodule. Short-term studies on the effect of cortisone on the reaction of the mouse peritoneum to quartz showed a delay in macrophage response (Curran, 1952) and an inhibition of fibrosis (Magarey and Gough, 1952 ; Schiller, 1953). Over a longer period the effect of cortisone has been observed on the development of fibrosis in rats injected intratracheally with 50 mg. of quartz (Harrison, King, Dale, and Sichel, 1952). Cortisone treatment decreased the mobility of dust-laden phagocytes, and the marked alteration in the distribution of dust throughout the lung modified the normal pattern of fibrosis. The fibrosis in the cortisone-treated animals was irregular, diffuse, and generally less.

In this paper we report the analyses of lungs for silica and collagen, and hilar lymph glands for silica, from the above experiment on rats. The amount of collagen gave an indication of the amount of fibrosis ; generally there was less in the cortisone group. The partition of silica between lung and lymph node gave a rough measure of macrophage activity. These analytical results confirmed previous histological findings.

This confirmation was not so marked when the same methods were applied to material from a later experiment in which King, Harrison, and Attygalle (1954) observed the effect of cortisone upon established silicosis. One hundred days after an intratracheal injection of quartz cortisone was given to a group of rats and the hormone treatment then continued regularly for 260 days. On histological examination the lungs of the cortisone-treated animals appeared similar to those of the controls, which had received quartz alone. The maximum grade of fibrosis was present in both groups 150 days after injection of the quartz, *i.e.*, 50 days after the start of cortisone treatment, and this picture persisted till the end of the experiment. Chemical examination, however, showed differences between the two groups.

Material

The material analysed was taken from rats used in the experiments of Harrison and others (1952) and King and others (1954). All animals had been injected intratracheally with 50 mg. of quartz dust.

Methods

Lungs and lymph glands were bulked into groups as shown in the Tables. Silica was estimated by weighing the acid-insoluble residue of the ash. Collagen was estimated by determining the hydroxyproline content of lung hydrolysates, non-collagenous material being removed by precipitation with trichloracetic acid (Janota, 1943 ; Harkness, 1952).

Preparation of Material.—Lymph glands were separated from the fixed lung, and lung and lymph glands were dried, bulked, and weighed. Remainders of blocks taken for sectioning were de-waxed and the dried tissue added to the groups. The bulked lungs were finally ground to a fine powder.

Silica Estimation.—A sample of material (containing about 10 mg. SiO_2) was weighed into a light (about 7 g.), hard glass centrifuge tube. The sample was ashed for 12 hours at 320° and then for 12 hours at 480° ; 2N–HCl (3 ml.) was added to the ash, and the mixture warmed, with occasional stirring, on a boiling water bath for 30 minutes. After centrifuging, the extraction with warm 2N–HCl was repeated and the residue finally extracted by agitation with cold 2N–HCl. The residue (SiO_2) was weighed after drying at 105°. Recoveries of known similar amounts of quartz were in the range of 93 to 98%.

Collagen Estimation.—A sample (100 mg.) of dried ground lung was weighed into a thick-walled hard glass test tube graduated at 10 ml. Fat was removed by ether extraction, water (5 ml.) was added, and the mixture autoclaved for six hours at 30 lb. pressure. Water was added to 10 ml. and the tube heated for 15 minutes on a water bath. The mixture was made up to 10 ml., centrifuged and filtered. To 5 ml. of filtrate was added an equal volume of 10% trichloracetic acid and the mixture filtered after standing for one hour. Then 5 ml. of filtrate was transferred to a 50 ml. beaker and evaporated almost to dryness on a water bath. The residue was taken up in 6N–HCl (2 ml.) and washed with acid (4 ml.) into a hard glass test tube. The tube was sealed and autoclaved for four hours at 40 lb. pressure. The contents of the tube were made up to 10 ml. with 6N–HCl, shaken with charcoal, and filtered. A sample of this hydrolysate, after neutralization with 6N–NaOH and further appropriate dilution with a neutral mixture of 6N–NaOH and 6N–HCl, was used for the estimation of hydroxyproline following the method outlined by Neuman and Logan (1950*a*, *b*).

Results

Nature of Reticulin and Lung Collagen.—Some information as to the nature of reticulin and lung collagen was obtained using the standardized technique of two-dimensional filter paper chromatography. Reticulin was isolated from human renal cortex (Randall, 1953). Eighty per cent. of the dried material dissolved on autoclaving for six hours at 30 lb. The solution was hydrolysed with 6N–HCl. The amino-acid compositions of the reticulin hydrolysate and of a rat lung collagen hydrolysate were compared chromatographically with the hydrolysate of a calculated amount of purified commercial gelatin prepared from skin collagen. There was good correspondence between the position and intensity of spots. Glycine, hydroxyproline, and proline, the major constituents of " standard " collagen, were prominent in all cases. An outline of the amino-acid patterns is shown in Fig. 1. Hydroxyproline, which gave a faint yellow-brown spot with ninhydrin, was more easily compared by the highly characteristic pink spot which appeared after treatment with isatin followed by Ehrlich's reagent (Jepson and Smith, 1953). The chromatographic evidence suggested that reticulin and lung collagen resembled the more widely known collagens (Tomlin, 1953).

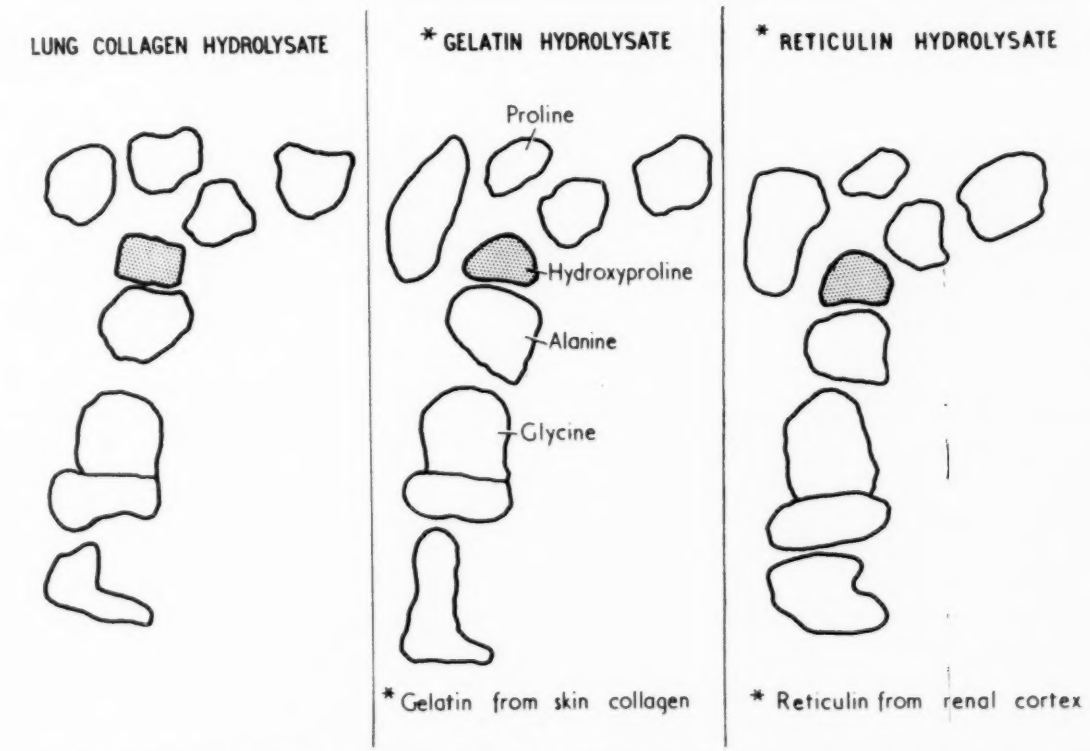

FIG. 1.—The amino-acid composition of lung and skin collagen and of reticulin. Outline of amino-acids in two-dimensional filter paper chromatograms of acid hydrolysates of lung collagen, gelatin from skin collagen, and reticulin. Hydroxyproline detected by the method of Jepson and Smith (1953).

TABLE 1

EFFECT OF CORTISONE ON THE MOVEMENT OF QUARTZ DUST FROM LUNGS TO LYMPH GLANDS IN DEVELOPING SILICOSIS

Duration of Experiment (days)	No. of Rats in Group	Weight of SiO_2 (mg./rat) in						% SiO_2 in Dried Lymph Glands	
		Lungs		Lymph Glands		Lungs + Glands			
		Control	Cortisone	Control	Cortisone	Control	Cortisone	Control	Cortisone
30	4	27	34	0·5	0·2	28	34	1·3	1·4
60	4	24	24	1·8	0·6	26	25	1·9	1·9
90	4	21	26	2·2	0·4	23	26	2·5	1·9
120	4	22	26	3·8	0·2	26	26	2·8	0·7
150	4	21	21	5·8	1·2	27	22	2·8	3·7
180	6	16	30	5·7	1·1	22	31	2·9	4·0
210	3	17	28	7·0	1·1	24	29	3·7	2·7
240	3	18	23	6·8	—	25	—	2·6	—

Cortisone and Developing Silicosis.—This was studied first in the lymph glands and secondly in the lungs.

Lymph Glands.—Nodes from the controls were larger (Fig. 2a) and contained more quartz dust (Table 1 and Fig. 2b) than the " cortisone " nodes.

Silica Content in Lung.—The difference in silica content of the lungs from the two groups (Table 1) was not as marked as in the case of the lymph glands. Nevertheless, the cortisone lungs tended to contain more dust than the controls.

Collagen Content in Lung.—Collagen estimations were carried out on the bulked groups of some lungs, and on those individual lungs, sections of which had been photographed in the original experiment (Harrison and others, 1952). The results (Table 2) indicated that in the later stages of the experiment more lung collagen was present in the control than in the cortisone-treated group.

Cortisone and Established Silicosis.—The distribution of collagen and silica tended to follow the same pattern as in the experiment on developing silicosis. Lymph nodes from the controls were larger and contained more silica (Table 3) than the " cortisone " nodes. Control lungs contained correspondingly smaller amounts of silica. Of the

TABLE 2

EFFECT OF CORTISONE ON DEVELOPING SILICOSIS

Duration of Experiment (days)	No. of Rats in Group	Control		Cortisone	
		Lung Collagen		Lung Collagen	
		mg./Rat	% Dry Basis	mg./Rat	% Dry Basis
7*	1	22	4·0	14	2·7
30	4	9·2	2·0	22	3·1
60	4	33	4·8	—	—
68*	1	33	3·2	20	2·9
90	4	42	5·2	38	5·3
103*	1	39	4·4	37	3·5
120	4	68	6·3	50	5·8
150	4	230	18	46	5·9
154*	1	89	8·8	34	5·0
180	6	140	14	72	6·4
202*	1	520	37	58	6·9
210	3	140	12	89	8·0
230*	1	320	24	130	10
240	3	400	25	120	12

*Individual lungs (sections photographed in original experiment), otherwise in bulked lungs.

TABLE 3

EFFECT OF CORTISONE ON ESTABLISHED SILICOSIS : MOVEMENT OF QUARTZ DUST FROM LUNGS TO LYMPH GLANDS AND COLLAGEN CONTENT OF LUNGS

Duration of Experiment (days) *	No. of Rats in Group		Weight of SiO_2 (mg./rat) in						Lung Collagen			
			Lungs		Lymph Glands		Lungs + Glands		Control		Cortisone	
	Control	Cortisone	Control	Cortisone	Control	Cortisone	Control	Cortisone	mg./Rat	% Dry Basis	mg./Rat	% Dry Basis
190	3	5	28	28	4·3	2·7	32	31	190	16	130	11
330	3	5	19	23	6·5	4·0	26	27	260	19	190	10
365	3	4	21	26	8·4	3·2	29	29	300	23	300	16

*Cortisone treatment begun at 100 days.

three batches of lungs analysed in each group, the first two in the control series contained more total collagen than those in the cortisone series.

Discussion

Cortisone and Developing Silicosis.—Fig. 2 shows the weights and silica contents of lymph glands from both groups plotted against time. The relatively small amount of silica in the cortisone lymph nodes provides convincing evidence that continued administration of the hormone has interfered with the mechanism normally responsible for the transport of dust particles from the lungs to the lymph nodes. This is also shown by the results in Fig. 3 where the cortisone lungs are seen to contain more silica than the controls.

Although there was much variation in the size of the lymph glands, the percentage of silica in the glands, in all cases, was fairly constant (Table 1).

Table 1 shows figures of total silica content and its distribution between lung and lymph glands. There is little difference between the cortisone and control groups for the totals; in fact, they are roughly the same in the two groups and remain surprisingly constant over the course of the experiment. The amount of silica originally given intratracheally to each animal was 50 mg., and about 50% of this was found in the respiratory system after the first month. In the cortisone series nearly all the silica remained in the lungs, whereas in the control group about 30% was transported to the lymph nodes after 200 days. (A control animal with lymph nodes of exceptional size was analysed

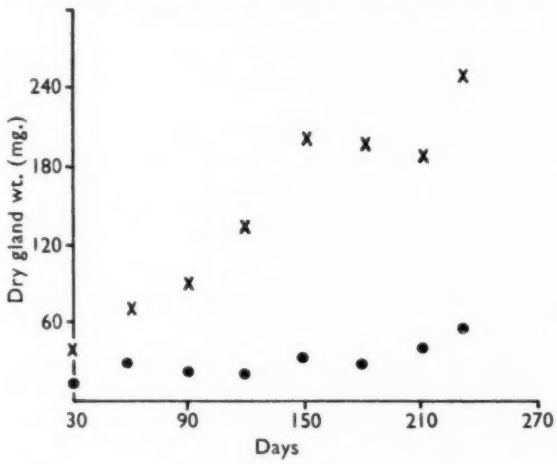

FIG. 2a

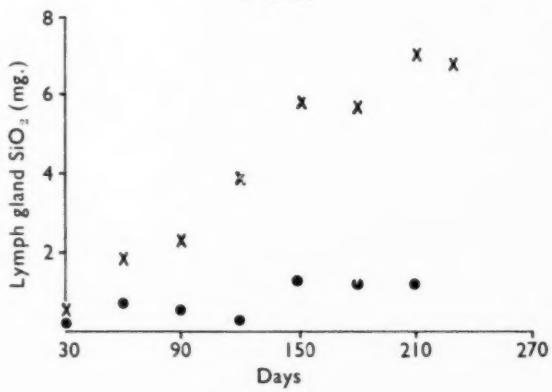

FIG. 2b

FIGS. 2a and 2b.—Cortisone and developing silicosis.
2a shows average dry weights of lymph glands.
2b shows average SiO_2 in lymph glands.
X Control quartz rats; ● Cortisone-treated quartz rats.

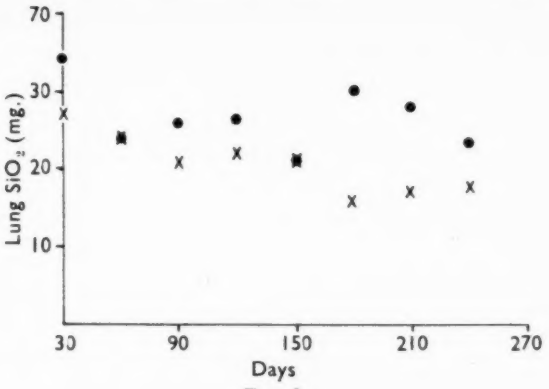

FIG. 3

FIG. 3.—Cortisone and developing silicosis: graph showing average SiO_2 in bulked lungs.
X Control quartz rats; ● Cortisone-treated quartz rats.

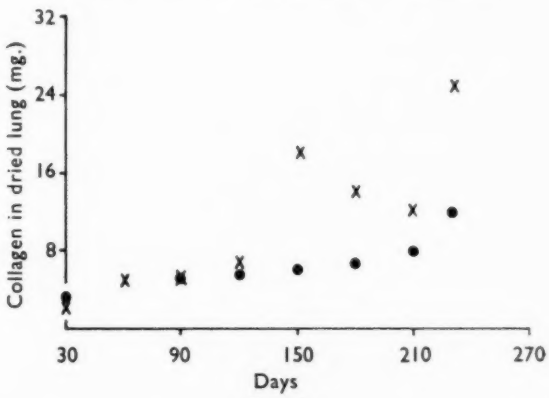

FIG. 4

FIG. 4.—Cortisone and developing silicosis: graph showing % collagen in bulked lungs.
X Control quartz rats; ● Cortisone-treated quartz rats.

separately : over 50% of the retained silica appeared in the lymph nodes.)

The results of the collagen estimations in the lungs show little difference between the two groups in the early phases of the experiment. After 150 days a difference appears (see Fig. 4), and the cortisone group has much less collagen than the control group. A similar impression was obtained histologically (Harrison and others, 1952), although decisive comparisons were difficult to make in some cases because of the diffuse, irregular pattern of fibrosis in the cortisone-treated animals.

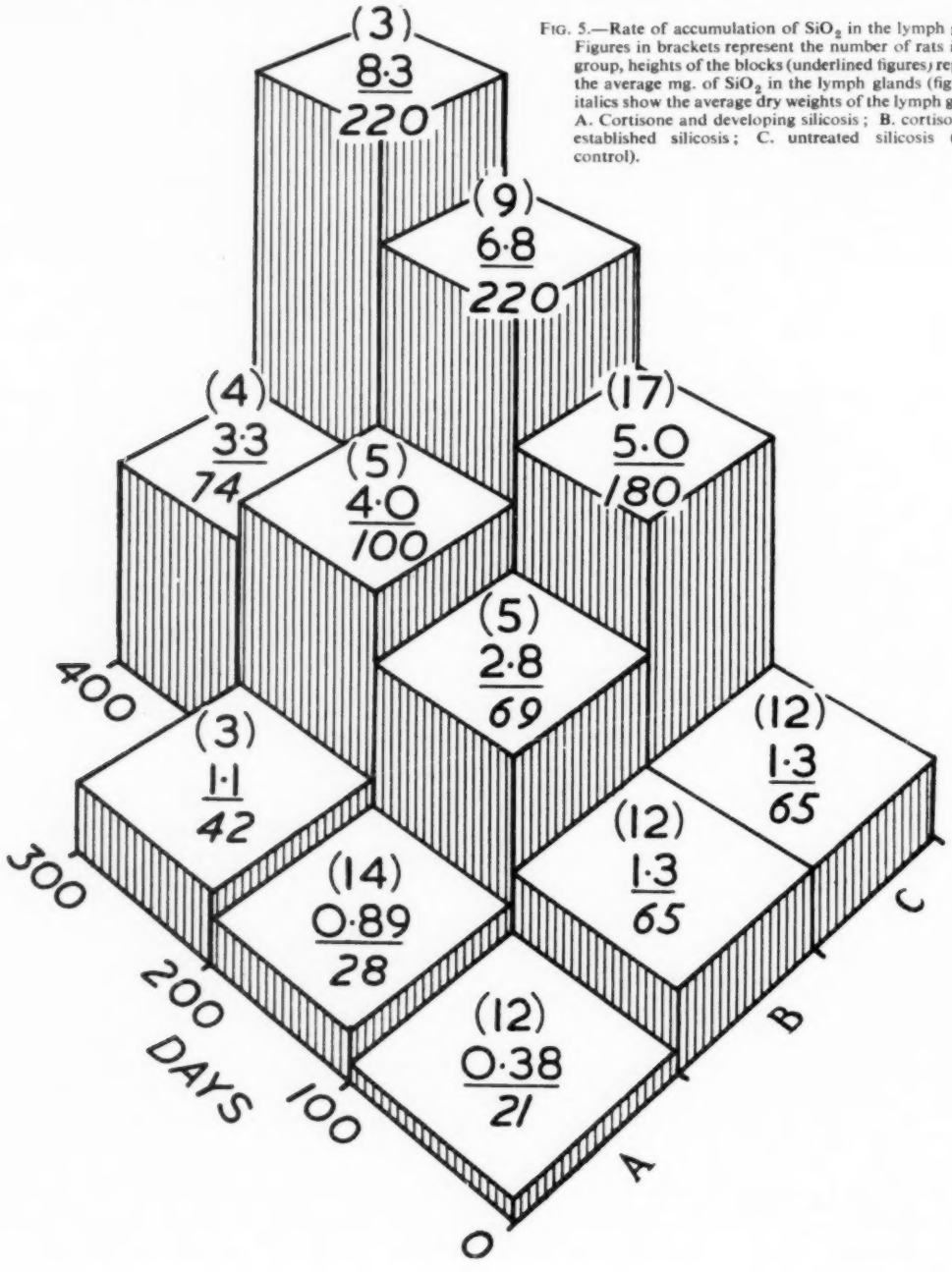

FIG. 5.—Rate of accumulation of SiO_2 in the lymph glands. Figures in brackets represent the number of rats in each group, heights of the blocks (underlined figures) represent the average mg. of SiO_2 in the lymph glands (figures in italics show the average dry weights of the lymph glands). A. Cortisone and developing silicosis ; B. cortisone and established silicosis ; C. untreated silicosis (quartz control).

A combination of chemical and histological methods for assessing fibrosis has also been recently reported by Aterman (1954). Estimating collagen by the chemical method described above, he found a satisfactory correlation between histological and chemical results in studying fibrosis produced in the liver by carbon tetrachloride. In these experiments, too, cortisone was found, at certain stages, to inhibit the formation of collagen.

Cortisone and Established Silicosis.—In the control animals there was, over the first 200 days following the injection of quartz, an almost linear increase with time in the amount of silica in the lymph nodes, indicating continuous regular phagocytic activity (Fig. 2b). If cortisone was given (see Table 3), this activity was depressed, and there was little increase of silica in the lymph nodes after the start of cortisone treatment. Indeed, further deposition of dust in the lymph glands was effectively inhibited throughout the whole period of cortisone administration. From tissue culture work, Paff and Stewart (1953) have made the general observation that " cortisone can effectively block the nomadic proclivities of the free wandering cell " (macrophage)—a conclusion which would seem to apply equally well to the above results.

As to fibrosis, it has been found histologically that the two groups are qualitatively similar (King and others, 1954), yet on a chemical basis the lungs of the controls tend to contain more collagen (Table 3). This discrepancy reflects the inadequacy of the histological method for measuring fibrosis quantitatively. Beyond the visual assessment, which at five months showed the maximum grade of fibrosis in both groups, the histological method could throw little light on further collagen formation. But the quantitative chemical estimation detects this further development, and thus yields results that show a difference between the two groups.

Studies *in vivo* (Wolbach, 1933) and *in vitro* (Porter and Vanamee, 1949 ; Porter, 1951 ; Gerarde and Jones, 1953) have led to the claim that collagen is a product of the metabolic activity of fibroblasts. The lower collagen values found in the treated group lend support to the thesis that cortisone modifies fibroblast activity.

Lymph gland results from both experiments are combined in Fig. 5. The heights of the blocks in this diagram represent lymph gland silica (mg. per rat) ; the average dry weights of glands and the number of animals in each block are also shown. That cortisone has exerted a marked effect on the dust content of lymph glands in both experiments is clearly demonstrated in this diagram.

Summary

The lungs of cortisone-treated and control silicotic rats have been analysed for silica and collagen, and the lymph glands for silica. The experiments tested the effect of cortisone on (*a*) developing and (*b*) established experimental silicosis.

In both experiments cortisone (*a*) decreased the transport of quartz dust from the lungs to the hilar lymph nodes, and (*b*) inhibited the formation of collagen in the lungs.

The results have been correlated with previous histological findings.

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THE DEVELOPMENT OF COMPENSATION FOR OCCUPATIONAL DISEASES OF THE LUNGS IN GREAT BRITAIN

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Throughout the world workmen's compensation or its equivalent has been a dominating influence on the manifold studies of the occupational dust diseases of the lungs—the pneumoconioses. The purpose of this contribution is to survey the origin and development of the relevant legislation in Great Britain. Such a historical review seems opportune and justified by reason of fundamental alterations and extensions which have recently taken place in Great Britain and in South Africa.

By the Workmens Compensation Act, 1897, a workman injured by accident arising out of and in the course of employment was enabled statutorily to recover compensation from his employer. No similar provision, however, was made in respect of occupational disease (except in those cases where the disease could be held to be due to an " accident ") until the Workmens Compensation Act, 1906, when certain industrial diseases, namely, anthrax, poisoning by lead, mercury, phosphorus, and arsenic, and ankylostomiasis were specifically included. By section 8 (6) power was given to the Secretary of State to bring other diseases under the Act.

At this date abundant evidence existed to suggest, if not prove, that certain other diseases were of occupational origin, in particular, those lung diseases known as miners' phthisis, stone-masons' phthisis, potters' asthma, grinders' rot, and ganister workers' disease and more generally as fibroid phthisis (Meiklejohn, 1949, 1951, and 1952). Indeed, this had been recognized officially as early as 1864, when a Royal Commission appointed to inquire into the serious mortality of workmen in metalliferous mines recorded the excessively high incidence of pulmonary disease among these workmen, in particular in the tin mines of Cornwall and in the lead mines of the north of England.

In 1892 a Departmental Committee reported similarly on the slate miners of Merionethshire and between 1896 and 1897 another committee revealed the seriousness of the same diseases in a variety of " dangerous trades " (Home Office, 1896, 1897).

Following observations by Dr. Robertshaw, a general practitioner at Stocksbridge near Sheffield, on the occurrence of pulmonary diseases among the local ganister miners, Dr. (later Sir Thomas) Legge undertook an enquiry, the results of which were published in 1901. An important recommendation was for the establishment of periodical medical examinations of ganister miners. In 1904 Haldane, Martin, and Thomas published their classic report on the health of Cornish tin miners.

Meanwhile attention was more closely focused on the problem by reports from South Africa of the alarming incidence of and mortality from miners' phthisis among miners in the developing Rand gold mines.

Allied to these diseases were certain cases of pulmonary affections in dock labourers engaged in handling cargoes of dusty grain, in flax workers exposed to the inhalation of fine fibres, and in chemical, iron, and brass workers exposed to the inhalation of irritant fumes.

Accordingly it is understandable that workmen through their trade unions immediately pressed to have these occupational diseases of the lungs included under the Act, in like manner to those already scheduled.

This was the background against which a Departmental Committee on Compensation for Industrial Diseases was appointed in 1906 under the chairmanship of Mr. Herbert Samuel (now Lord Samuel) " to enquire and report what diseases and injuries, other than injuries by accident, are due to industrial

occupations, are distinguishable as such, and can properly be added to the diseases enumerated in the Third Schedule of the Workmen's Compensation Bill, 1906 ". The report was published in May, 1907 (Departmental Committee on Compensation for Industrial Diseases, 1907).

To decide which diseases might properly be recognized as of occupational origin the Committee, first of all, defined three principles of selection. (1) Is it outside the category of accidents and diseases already covered by the Act ? (2) Does it incapacitate from work for a period of more than one week, which is the minimum period for which compensation is payable under the Act ? (3) Is it so specific to the employment that the causation of the disease or injury by the employment can be established in individual cases ?

The Committee added that this test was subject to the qualification that for a disease which was common in a particular trade and existed, though very rarely, outside the trade, it might be right to make that disease the subject of compensation.

These principles of selection were reviewed and endorsed in 1933 by a similar departmental committee under the chairmanship of Sir Humphry Rolleston, which was appointed to inquire and report on certain proposed extensions of the schedule of industrial diseases under the Workmens Compensation Act, 1925 (Home Office, 1933).

In our present historical purpose only the third principle of selection is important ; and relevant to this the following conclusions of the 1906 Committee are significant :

> " (1) Both fibroid phthisis uncomplicated and fibroid phthisis with the supervention of tubercle are in their nature occupational diseases.
>
> " Moreover, there is little doubt that ordinary tuberculous phthisis prevails excessively among workers in gritty dusts, and this excess is in some measure due to the injurious influence of such dust on the lungs of workmen.
>
> " (2) Fibroid phthisis is a specific trade disease in grinders, certain potters, masons, tin miners and ganister miners. On the principles of the Workmens Compensation Act, 1906, the employers might properly be required to pay compensation to their workpeople who contract it."

Having regard to the present situation in which pneumoconiosis of coal workers dominates the field, the following comment is of considerable interest.

> " We are clearly of opinion that coal miners are not liable to fibroid phthisis, and although cases of anthracosis, using the term to mean cases in which the lung is charged with coal dust, are commonly met with, we cannot find that in any one that condition has proved to be a contributory cause of death.
>
> " (3) Ordinary tuberculous phthisis cannot, of course, be regarded as a disease specific to any employment."

Notwithstanding these explicit opinions, the Committee felt unable to recommend the addition of fibroid phthisis to the schedule. The chief arguments which influenced them in this decision were the difficulty of diagnosis of the disease even by experts, and, in the early stages particularly, the differentiation from fibroid phthisis of other origin, and chronic bronchitis with " asthma " or technically, emphysema.

Relevant to this, however, it is important to note that at this date, though experiments were in progress, radiographic examination of the lungs had not yet been established as an aid to diagnosis in pulmonary diseases.

These findings of the Committee meant that the workmen had failed in their immediate purpose but they had established in official records that fibroid phthisis was an occupational disease of workmen in certain trades and occupations. The need was to overcome the difficulties of diagnosis in individual cases.

Some help was immediately forthcoming for in the same year, 1907, Summons published a report upon an investigation into miners' phthisis at the gold mines at Bendigo, Australia, in which he advocated the use and value of *x*-ray examination of the lungs in diagnosis.

Then in 1912 appeared a Report of a Commission on Miners' Phthisis and Pulmonary Tuberculosis within the Union of South Africa, and this was the basis of the Miners Phthisis Act, 1912. As this Act marks the beginning of compensation legislation for dust disease of the lungs it is worthy of remark that from the very outset in South Africa the legislation was primarily directed to preventing the disease by control of the production of dust and deleterious environmental conditions, and only secondarily to mitigate the effects of the disease in individual patients, through suspension of the workman from dangerous processes and payment of compensation. Towards this purpose a scheme of " benefits " examinations of Europeans by " a panel of medical examiners " was instituted.

During the five years 1912–1916, 6,472 patients received benefit, that is compensation, awards and were compulsorily suspended from further employment as miners.

The whole subject of occupational phthisis in Great Britain was reviewed to date in the Second Report of the Royal Commission on Metalliferous Mines and Quarries, 1914. From this it appears that, on behalf of the Commissioners, Professor Beattie of Sheffield University carried out a series of

dusting experiments in animals and these proved the peculiarly injurious character of siliceous dust. The Commissioners recorded :

> " We are further of opinion that inorganic dusts may be grouped in two classes :
>
> " (1) Dusts the inhalation of which has not so far been shown to be associated with any marked increased mortality from respiratory diseases ; to this class belong coal, shale, slate, iron ore, clay, limestone, plaster of Paris, and cement.
>
> " (2) Dusts the inhalation of which is associated with excessive mortality from respiratory diseases and especially from phthisis ; to this class belong quartz, quartzite (i.e. ganister and buhrstone), flint, and sandstone."

In the following year, 1915, Dr. E. L. Collis, one of H.M. medical inspectors of factories, delivered the Milroy Lectures at the Royal College of Physicians, London, on " Industrial Pneumonoconioses with Special Reference to Dust Phthisis ". By summarizing existing knowledge and presenting the results of his researches he fixed attention on the role of free crystalline silica in causing the disease. No single contribution had greater influence in defining the immediate trend of research and legislation for silicosis in Great Britain.

Miners' Phthisis in South Africa

Meanwhile practical guidance was forthcoming from South Africa, where a Select Committee had been enquiring into the working of the Miners Phthisis Acts. Evidence presented to them revealed that the system of examinations by a panel of medical examiners was unsatisfactory chiefly because of the lack of uniformity in standards of diagnosis by different members. Furthermore the absence of a system of periodical examinations hindered the detection of new cases in the early non-disabling stages of the disease.

The Committee made recommendations for improving the system and these are noteworthy for the priority and emphasis attached to preventive measures in the mines. In relation to the medical aspects the following are important recommendations : (1) The establishment of a central bureau specially organized for the purpose of directing and, where necessary, conducting all medical examinations of miners ; (2) initial medical examination of all men making application for underground work ; (3) periodical medical examination, at six-monthly intervals, of all miners, with the object of excluding from underground work all men suffering from tuberculosis ; (4) *x*-ray examination in every case as an additional means of ascertaining whether, or in what degree, an applicant for compensation or any other person is afflicted with the disease ; (5) a system of necropsy examinations, reports, and records by the Director of the South African Institute of Medical Research ; (6) the establishment of industries with the special object of employing beneficiaries. In relation to this recommendation the Committee observed that " monthly cash benefits to beneficiaries are less beneficial than the finding of employment " ; (7) compulsory exclusion from underground work of all persons suffering from active tuberculosis, these workmen to receive compensation for loss of employment.

Arising out of this Report (South African Miners' Phthisis Prevention Committee, 1916) the Miners' Phthisis Medical Bureau consisting of a chairman and full-time medical officers was constituted by Act of Parliament in August, 1916. The Medical Bureau was concerned solely with the medical provisions of the Act and was directly responsible to the Minister of Mines.

This development may be regarded as the critical point of emergence in compensation for miners' phthisis or, as it became, silicosis.

So it appears that throughout the world silicosis was accepted as an occupational disease in certain industries and processes. Radiographic examination of the lungs had been established and appeared to resolve, at least partly, the difficulties of diagnosis. Indeed in 1916 the Miners' Phthisis Prevention Committee in South Africa had recorded that " the radiographic appearances in cases of silicosis afford the most reliable *single* piece of evidence in establishing the existence and the actual stage of the disease in any particular case ". On the administrative side the experience gained in South Africa between 1912 and 1916 was available to guide other countries.

The Workmens Compensation (Silicosis) Act, 1918

The foregoing are some of the factors which helped to initiate legislation in Great Britain, namely, the Workmens Compensation (Silicosis) Act, 1918. This Act empowered the Secretary of State to make schemes " for the payment of compensation by the employers of workmen in any specified industry or process or group of industries or processes involving exposure to silica dust, who are certified to have suffered death or total disablement from silicosis or silicosis accompanied by tuberculosis, or who, though not totally disabled, are found on medical examination to be suffering from silicosis or silicosis accompanied by tuberculosis to such a degree as to make it dangerous to continue work in the industry and are for that reason suspended from employment ".

In this rather involved legal phraseology the significant concepts to note are exposure to *silica* dust ; the conjoining of silicosis with tuberculosis ; the disease present to such a degree as to make it dangerous for the workman to continue in the risk ; and the receipt of compensation conditional on permanent suspension from employment in the dangerous processes.

It appears, however, that the Government did not consider silicosis to be a disease suitable for inclusion simpliciter in the Third Schedule to the Workmens Compensation Act, 1906. The necessary medical and administrative arrangements were too complex for this procedure ; the need was for special schemes.

In pursuance of the Act a scheme, the Refractories Industries (Silicosis) Scheme, 1919, was made and came into force on February 1, 1919 (Home Office, 1924).

The Scheme did not include any definition of silicosis, but in view of the antecedent discussions it obviously was intended to signify fibroid phthisis associated with work in certain industries and processes. The refractories industries were defined as " the following processes carried on at mines, quarries, factories and workshops at which refractory material containing not less than 80% of silica (SiO_2) is got or manipulated with a view to manufacture or sale ".

This precise figure of 80% silica, later elucidated as meaning total silica and not free silica, has frequently been interpreted as signifying that this level of silica content is necessary to the production of silicosis and by inference that lower percentages are " safe ". These conclusions are wrong. The purpose of naming this precise figure was to define the specific group of industries, well recognized in the trade, and to distinguish them from the fireclay industries, which the Scheme was not intended to cover.

For silicosis accompanied by tuberculosis the payment of compensation was limited to cases in which " the silicosis was so far advanced as to make the workman specially liable to tuberculosis or though not so far advanced was likely to accelerate materially the progress of the disease ". This abstruse provision immediately gave rise to difficulties of interpretation, and, having proved impracticable, was amended by Order in 1920 to " silicosis accompanied by tuberculosis " and without qualification.

To exclude workmen whose lungs were already damaged by any disease or who were otherwise not physically fit and so considered more susceptible to the effects of dust, the Scheme prescribed initial medical examination of new entrants. All workmen, except as noted below, so long as they were employed in scheduled processes, were required to submit themselves to periodical medical examination. If found to be suffering from silicosis or silicosis accompanied by tuberculosis they were compulsorily and permanently suspended from all work in the processes. It was, however, a serious defect of the Scheme that this provision did not apply in cases of simple tuberculosis. Moreover the absence of routine radiographic examination rendered the examinations ineffective as the disease was not detected in the early stages. In the case of workmen, who, at the beginning of the Scheme, had been employed for 20 years or more in the industries, submission to periodical examination was voluntary. This exception was considered necessary because it was realized that such workmen, if suspended, would probably have difficulty in obtaining alternative employment.

It is important here to remark that the Scheme required that the periodical examinations should be carried out at the mines, quarries, and brickworks, so that the examining doctors would gain first-hand knowledge and experience of the actual processes and incidental environmental conditions.

Arrangements were also made for the examination and certification of workmen suspected to be suffering from the disease and for re-examination, within specified intervals, of every workman in receipt of weekly payments as partial compensation. This requirement recognized that the disease was progressive in some cases and might result in increased disability necessitating review of the compensation award. These home visits to disabled patients again had the value that they enabled the doctors to study the social and economic problems incidental to the disease.

The medical examinations were reserved to specially appointed medical officers ; these were tuberculosis officers with special experience of the disease in their own area of practice. For the disposal of difficult cases arrangements were provided for reference to medical advisory committees or medical referees. These committees consisted of three members, two nominated by the local university, while the third was either the medical officer of health for the county or a chief tuberculosis officer not engaged in making the actual examinations. In those areas where cases only arose sporadically the duties were assigned to a single medical referee appointed for the area.

X-ray examination of the chest was not normally required even in compensation cases ; such examination was entirely at the discretion of the medical officer but was compulsory in cases referred for the

decision of the Medical Advisory Committee. The medical certificate when issued was final and conclusive of the matters certified, which means that there was no appeal against the decision. In the great majority of cases the appointed medical officer exercised sole authority : in cases referred to the Medical Advisory Committee their decision was effective. As already stated certification involved permanent suspension of the workman from the industries. It was competent for the medical officers while certifying that a workman was suffering from the disease to certify further that the general physical capacity for employment of the said workman was not impaired. In such cases a scheme of modified compensation payments was provided for a period, so long as the workman remained out of employment, but not exceeding 13 weeks (Treasury, 1951). Moreover, it should be emphasized that compensation was payable only in respect of disablement caused by the disease. The amount of compensation was dependent on ascertained loss of earnings and subject to a prescribed maximum weekly payment.

In fatal cases a post-mortem examination, made by or in the presence of the appointed medical officer, was required as an essential part of any compensation claim unless, at the date of death, the deceased workman had been in receipt of weekly payments of compensation. This examination also enabled the doctors to correlate the pathological changes with their clinical and radiographic findings.

The liability to pay compensation was laid on the employer but a General Compensation Fund was compulsorily maintained by levies contributed by all employers in the industries. At the same time effective measures to control the production of dust were prescribed by regulations and these preventive supporting measures became an integral part of all subsequent legislation.

Thus had Great Britain followed the lead of South Africa by enacting legislation, admittedly restricted, to provide compensation for disablement and death from silicosis.

Meanwhile in the silver, lead, and zinc mines at Broken Hill, New South Wales, a miners' strike began on May 19, 1919, and continued until November 10, 1920 (George, 1947). Among the terms of settlement were the following conditions : (*a*) withdrawal from the industry of all workers found to be suffering from either tuberculosis or pneumonoconiosis ; (*b*) compensation of all workers found suffering from these diseases ; and (*c*) medical examination of all workers before entering or re-entering the industry.

Review of Operation of Refractories Industries (Silicosis) Scheme, 1919

The Refractories Industries (Silicosis) Scheme, 1919, was an interesting experiment in workmen's compensation for a specific industrial disease but experience of its operation soon revealed serious defects. Almost exactly four years after its beginnings a Departmental Committee was appointed in February, 1923, (1) to inquire into the working of the Scheme for the Refractories Industries under the Workmens Compensation (Silicosis) Act, 1918 ; and (2) to advise on any proposals for applying the Act to other industries which might be referred to it by the Secretary of State.

In the Report which was published in 1924 the Committee recorded that their enquiries had revealed certain important defects in the provisions and administration of the Scheme. The most serious shortcomings were the absence of power to suspend persons suffering from tuberculosis unaccompanied by silicosis, lack of uniformity in the medical examinations, and failure to exclude workmen showing signs of the disease before they became disabled. The Committee found also that the appointed medical officers had failed to use their powers to obtain a radiograph of the chest : only 2·5% of the cases examined included *x*-ray examination. Having regard to the difficulties of diagnosis except perhaps in advanced cases the Committee stated that " it is throwing a great and, we believe, unwarrantable burden upon an appointed medical officer to allow him even after considerable experience of the disease, to exercise on his sole responsibility the supreme power of suspension, especially as a certificate given by an appointed medical officer means that there is no possibility of appeal from his decision. Much more is this so when, as under present arrangements, there is no guarantee that the appointed medical officer has had any previous experience of the disease before taking up his duties ".

Among the witnesses examined, Dr. F. Coutts, of the Ministry of Health (tuberculosis division), argued against reserving the work to a medical board of full-time doctors as in South Africa. He submitted that the strength of the medical board might be attained without the dissociation of the silicosis work from that of tuberculosis officers. The Report quotes Dr. Coutts as follows :

> " In his opinion such dissociation would be a loss to tuberculosis officers, seeing that the two diseases have such close relations to each other. It would also tend in his opinion to lessen the number of medical men having any knowledge of silicosis, and would thus reduce the field from which future specialists in silicosis could be drawn when vacancies occurred."

The Committee found that Dr. Coutts' scheme involved practical difficulties which outweighed its possible advantages. The most important difficulties would be the difference in experience between the full-time silicosis expert and the tuberculosis officer and in completing periodical medical examinations at widely scattered works.

Finally the Committee made certain recommendations which included the establishment of a medical board consisting of two whole-time medical officers with a centre at Sheffield, these doctors to be responsible for all medical examinations, except certain initial examinations, under the Scheme. A greater use of radiographic examinations for diagnosis was considered necessary and the responsibility of suspending a workman on account of silicosis, it was considered, should not devolve on one medical officer. They also advised that power should be given to medical officers to suspend from further employment in the industries any workman found to be suffering from tuberculosis of the lungs whether accompanied by silicosis or not.

By these measures the Committee were of opinion that a satisfactory scheme for compensation would be provided for the refractories industries and form a suitable basis on which to frame other schemes.

Consequent Legislation

The Government gave effect to the Committee's recommendations in the Refractories Industries (Silicosis) Scheme, 1925, in which the most notable change was the establishment of the medical board of full-time medical officers to be appointed by and to hold office on such terms as might be prescribed by the Secretary of State. Their duties comprised initial, periodical, and compensation examinations and the arrangement of post-mortem examinations in death claims.

The following provisions are important :

> " The Medical Board shall have power in any case where they consider necessary to make or cause to be made a radiographic examination of the lungs of the workman and to obtain the opinion of a radiologist on the case."

Radiographic examination of the chest, it will be noted, was not made an indispensable part of every case, even in compensation claims, but the terms of the antecedent report implied that wide use of this power should be made by the medical board.

Section 32 enacted that :

> " All workmen employed in the industries shall be examined by one or more officers of the Medical Board at the prescribed intervals, and if on such examination it appears to the Medical Board that the workman is suffering from silicosis or silicosis accompanied by tuberculosis *to such a degree as to make it dangerous for him to continue work in the industries*, the Board shall suspend the workman from further employment in the industries, and shall certify accordingly in the prescribed form.
>
> " Provided that the foregoing provision shall not apply to any workman employed at the 1st February, 1919, in the industries, who had at that date been so employed for more than twenty years and has since then continued to be so employed, except on the written request of the workman."

Particularly significant is the qualification which I have placed in italics, also the fact that long-service workmen were excluded from compulsory suspension, thereby recognizing their difficulty in securing alternative employment.

The Report had anticipated the need for similar schemes for other industries and processes and to this end section 47 of the Workmens Compensation Act, 1925, conferred powers on the Secretary of State to make such schemes as circumstances arose.

Schemes for Other Industries

Metal-Grinding Industries.—The Metal Grinding Industries (Silicosis) Scheme was made in April, 1927. For various reasons, including serious trade depression in one section of the industries, heavy expenditure entailed by compliance with new regulations for the suppression of dust, and the change over from sandstone grindstones to manufactured abrasive wheels of non-siliceous materials, this scheme did not repeat the pattern of the refractories scheme but was limited substantially to the provisions of the Workmens Compensation Act relating to scheduled industrial diseases. Thus the Scheme was entirely restricted to compensation and did not include arrangements for initial or periodical examinations of men at work. Moreover compensation was provided only in respect of total disablement or death by reason of the disease. Certification was not by the medical board but by the certifying surgeon appointed under the Factory and Workshop Act, 1901, subject to appeal by an aggrieved employer or workman to a medical referee, whose decision was final.

In the making of this scheme there emerged a situation of considerable interest and very disturbing in its import. The scheme was made on April 30, 1927, and ordered that :

> " This Scheme shall come into force on 1st July, 1927, and shall apply to all *workmen employed at any time on or after that date* in the following processes . . . (author's italics)."

In what followed the critical consideration was the definition of a grindstone :

> " Grindstone means a grindstone composed of natural or manufactured sandstone, but does not

include a metal wheel or cylinder into which blocks of natural sandstone or manufactured sandstone are fitted."

In effect this means that the employers were given two months' advance warning of their liability to pay compensation. During this period hundreds of men were stood off work while sandstone wheels were replaced by wheels composed of non-siliceous abrasives, carborundum and emery. This happened despite previous protests by the employers that these substitutes were unsuitable for the work. While this action accelerated prevention of the disease, it had the purpose and effect that on resumption of work after the effective date of the Scheme, the workmen were outside the benefits of the Scheme and many employers avoided their liability to pay compensation. By this salutary experience the legislators learned to avoid this error in future schemes.

Pottery Industry.—Excessive mortality from phthisis and diseases of the respiratory organs in pottery workers, though long popularly recognized, was only officially recorded and emphasized by Dr. Farr in the Thirty-eighth Annual Report of the Registrar General for 1875, published in 1877. The situation was later confirmed in 1893 by a Home Office committee which enquired into the health conditions in the pottery trades. The facts were acknowledged by the Samuel Committee of 1906, and in 1908 a Committee recommended an annual examination for all workers (women and young persons) employed in emptying and scouring biscuit ware which had been fired in powdered flint. These examinations by the certifying surgeon were instituted in 1913 but proved ineffectual, as among 3,886 examinations completed up to 1928 there was not a single suspension on account of the disease. This was not because cases of the disease did not exist but because the examinations were entirely inadequate.

In 1923 the General Council of the Trades Union Congress requested the Secretary of State to schedule " potters' asthma " (silicosis) as an industrial disease under the Workmens Compensation Act. Decision, however, was deferred until inquiry could be made into the occurrence and incidence of the disease in the industry generally and in the separate trades. Dr. C. L. Sutherland and Dr. S. Bryson—the full-time officers of the Medical Board under the Refractories Industries Scheme—duly completed this inquiry and presented a report in 1926. The Secretary of State in 1927 appointed the 1923 Committee* (reconstituted) " to advise on a proposal for a scheme of compensation for the pottery industry and also to report whether any, and if so what, further precautionary measures are practicable for the prevention of silicosis in that industry " (Home Office, 1928).

From the evidence given by the employers and workmen it appeared that the need for a scheme was not seriously disputed. The problem, however, was to agree the extent of the provisions and define the arrangements necessary to fulfil them. As already described there existed at this date two separate types of scheme : first the Refractories Industries (Silicosis) Scheme, 1925, involving a general compensation fund maintained by levies from all the employers in the industries, joint committees responsible for the administration and a full-time medical board of two doctors ; secondly the Metal Grinding Industries (Silicosis) Scheme, 1927, which operated in accordance with the provisions of the Workmens Compensation Act for scheduled industrial diseases and comprising the duties of the certifying surgeons and the medical referees.

The Committee favoured the former plan but were hindered by the unwillingness of the employers to establish a general compensation fund, which would assure the payment of compensation when awarded and the payment of the incidental administrative and medical expenses.

Suspension of affected workmen at periodical examination posed a further problem, for generally these were skilled craftsmen, who would be difficult to replace and for whom opportunities of alternative work of similar status were exceedingly rare either in the industry or in the locality.

After considerable deliberation the Committee recommended that the right to and the conditions of compensation should follow those contained in the Metal Grinding Industries (Silicosis) Scheme, 1927, with the important modification that compensation should be payable for *partial* disablement by the disease. They recommended a medical board of whole-time medical officers. In the absence of a general compensation fund they advised a system of fees payable by employers and workmen for the various services, initial, periodical, claims, and *x*-ray examinations and certificates. The Committee accepted that undue disturbance of the work of the pottery industry would result if skilled workmen were subject to compulsory suspension for silicosis but observed that this difficulty did not apply in unskilled or semi-skilled workmen. Despite expert opinion on behalf of the employers, the Committee adhered to the established principle that suspension should be compulsory in all cases of

* Originally appointed to enquire into the Refractories Industries Scheme.

tuberculosis whether accompanied by silicosis or not. Again acceptance of compensation by any workman involved permanent suspension from the industry and also, save by forfeit of his compensation, from all other industries involving exposure to silica dust, whereby his condition might be aggravated.

As to the stage of silicosis at which it was considered dangerous for a workman to continue in the dangerous processes the Committee affirmed the findings of their First Report (1924) : " the time at which this occurs should be regarded as *the earliest stage* at which the disease can be diagnosed " (author's italics).

It is clear that they did not regard this stage as necessarily implying any degree of disability whatsoever, but simply the recognition of identifiable changes in the lungs involving characteristic radiographic nodular opacities and without regard to their extent.

Various Industries

A stage had now been reached at which it was possible to extend the legislation to cover a wider range of industries and processes. The Various Industries (Silicosis) Scheme, 1928, was made with effect from January 1, 1929. This was an omnibus scheme embracing among other processes the mining and quarrying of silica rock, drilling and blasting in silica rock, in or incidental to the mining or quarrying of other minerals, the crushing and grinding of siliceous materials, and certain defined processes in steel foundries and metal works, in potteries and in tin mines. Here the important matters to note are the narrow prescription of occupations and processes and the emphasis on silica rock, which, by definition, did not include any rock containing less than 50% free silica. This definition immediately caused practical administrative difficulties, particularly in claims among underground workers in coal mines. Indeed in December, 1930, the Scheme was amended so as to delete the qualification " less than 50% free silica ". This was the first occasion on which coal miners were included but only a very small group, namely, men engaged in drilling and blasting in silica rock incidental to the getting of coal. In other words only rockmen, otherwise denominated hard-headers, crutters, rippers and brushers, were included ; all others, such as coal-face workers, were excluded.

The machinery of operation was as in the Metal Grinding Industries (Silicosis) Scheme, 1927, that is, in accordance with the Workmens Compensation Act as applied to scheduled diseases.

Sandstone Industry

By this time Dr. C. L. Sutherland and Dr. S. Bryson, following an inquiry, had presented a Report on the Occurrence of Silicosis among sandstone Workers (1929). This led almost immediately to the Sandstone Industry (Silicosis) Scheme, 1929, which title is rather misleading, as the Scheme dealt only with the quarrying side of the trade and did not concern building operations other than those carried out at premises worked in conjunction with a mine or quarry.

As the employers accepted a general compensation fund the Scheme followed the pattern of the Refractories Industries (Silicosis) Scheme, 1925, and the Medical Board of two full-time medical officers became responsible for discharging the medical arrangements in both industries.

Silicosis (Medical Arrangements) Committee

The Home Office, the Department of State then responsible for industrial diseases, realizing that the existing sehemes marked only the beginning, prepared for future developments by appointing, in December, 1928, a committee under the chairmanship of Dr. J. C. Bridge, " to advise as to the medical arrangements which could be made for the diagnosis of silicosis (including silicosis accompanied by tuberculosis) in cases of claims arising under the Workmens Compensation Act, and for carrying out any periodic or other medical examinations of workers, which may be prescribed for any industry or process involving risk of silicosis under the Factory and Workshop Act, 1901, or any other enactment " (Home Office, 1929).

The Report was presented to Parliament on September 17, 1929. The Committee comprehensively reviewed the problems of diagnosis of the disease and the administrative arrangements necessary to meet them. As to diagnosis, they formed the opinion that " the basis of any arrangements in cases of claims to compensation for this disease and for carrying out any periodical medical examination of workers exposed to the risk must take the form of medical boards consisting of officers who devote their whole time to the work ".

It was foreseen that an increase of the work might involve the establishment of several medical boards at widely separated areas. In such circumstances previous experience had demonstrated the difficulty of maintaining uniform standards. To meet this situation the Committee advised the appointment of a chief medical officer at the Central Bureau to coordinate the work and maintain uniform standards. They again underlined the need for full use of

radiographic examinations, which meantime had been greatly improved under the Tuberculosis Service. Indeed, so impressed were they by this advance that they recommended that the *x*-ray facilities available in tuberculosis clinics should be made full use of by the Medical Board, and not only for the quality of the radiographs, but to maintain a link with the tuberculosis officers. Finally they emphasized the value of post-mortem examinations, which " afford conclusive evidence in the diagnosis of silicosis ". They considered that the Medical Board should be present, even though they did not perform the examination. When not present they recommended that the medical practitioner who conducted the necropsy should send them the organs affected together with a full report of the examination.

Having regard to the situation which was to emerge in the middle 1930s, the following comments are significant :

> " There is the question of the action of mixed dusts, including silica, and also the question of the influence of other dusts on lungs which have already been affected by silica as, for instance, the apparent effect of the inhalation of coal dust on a lung affected by the inhalation of silica dust " and " we feel that research should embrace not only silicosis but the pneumonoconioses in general."

As will soon appear this Report had an important influence in defining the comprehensive series of schemes which were to follow in 1931.

More Occupational Studies

A Report on the Occurrence of Silicosis amongst Granite Workers (Sutherland, Bryson, and Keating, 1930), which appeared in May, 1930, confirmed the occurrence of silicosis in the occupations of crushing and masoning. In the following month a similar report on the slate industry in Carnarvonshire (Sutherland and Bryson, 1930) recorded that there was evidence of silicosis among millmen but not in other occupations.

So far silicosis was the only form of occupational disease of the lungs which had been accepted as proved : the whole emphasis was on quartz, free crystalline silica (SiO_2). However, in 1930, following a very extensive and searching investigation, Merewether and Price published their findings on the " Occurrence of Pulmonary Fibrosis and Other Pulmonary Affections in Asbestos Workers ". The disease was asbestosis due to the inhalation of minute asbestos fibres—a complex silicate—combined silica. Moreover the term pulmonary fibrosis or, as it became, fibrosis of the lungs, was destined to occupy a significant place in future schemes.

Consolidating the Experience

So far as the compensation aspects were concerned, there now existed a substantial body of authoritative knowledge and experience. The need was to consolidate this in general legislation and so diminish further piecemeal extension. The various medical inquiries had established the occurrence of silicosis and of asbestosis in certain industries and occupations. Contemporaneous advances in chest radiology had provided a valuable—though still imperfect—objective aid to diagnosis. Experience in South Africa and in Great Britain had developed a workable system of medical arrangements and of administrative machinery for the payment of compensation.

The prospective legislation, however, required wider powers than existed. These were obtained in the Workmens Compensation (Silicosis and Asbestosis) Act, 1930.

> " An Act to extend section forty-seven of the Workmen's Compensation Act, 1925, to industries involving exposure to asbestos dust, and to amend the provisions of that section relating to medical arrangements and examinations."

Almost immediately and with effect from June 1, 1931, the Secretary of State, in pursuance of these powers, made new schemes for the refractories, sandstone, metal grinding, various and asbestos industries.

The Various Industries Scheme comprised a wider range of occupations and processes than hitherto, e.g., the getting and manipulation of granite (including any igneous rock) but the prescription of occupations and processes remained narrow. Precise definition, however, was necessary to minimize actions in the courts. Furthermore it should be noted that the schemes only gave the right to compensation to workmen employed in the prescribed industries or processes on or after the operative date of the individual schemes. However, there was an important restriction (excepting the refractories industries), namely that no compensation was payable " in cases where the workman has not been employed in the industry or process . . . at any time within the three years previous to the date of injury ".

The date of injury was the certified date of disablement and suspension or where the workman died, without having been previously certified and suspended, the date of death.

The purpose for this qualification was to limit the period during which it was considered reasonable that employers should be required to insure workmen after leaving their employment.

For many reasons, including failure by private

doctors to identify the disease when present in some cases and in others where the disease did not become manifest for several years after ceasing work in the risk, this restriction caused hardship and bitter controversy. In 1939 the period was extended to five years and in 1948 under the Industrial Injuries Act, when the State became entirely responsible for payments, the restriction was abolished.

Medical Arrangements

The fundamental change was in the system for medical examinations and certification. Previously, as described, each scheme included its own medical arrangements but all were now unified under the Silicosis and Asbestosis (Medical Arrangements) Scheme, 1931, which embodied many of the recommendations made in 1929 by the Silicosis (Medical Arrangements) Committee.

All examinations (except certain initial examinations by appointed tuberculosis officers) were reserved to a medical board of full-time medical officers. Due to the considerable extension of the work, boards, each of two members, were established at Sheffield, Bristol, Newcastle-upon-Tyne, and Stoke-on-Trent. These centres were chosen because they were focal points in areas in which the main causative industries were located and from which the majority of cases would derive. Sheffield was named as the headquarters and Dr. C. L. Sutherland, with his office there, was appointed Chief Medical Officer.

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The Medical Board's powers of suspension at periodical medical examinations, which did not necessarily include *x*-ray examination, also differed, except in cases of tuberculosis of the lungs, in the separate industries. For reasons already discussed skilled craftsmen in the pottery industry had the option, following advice in a confidential letter, and on written application, to continue at work and this applied in a modified way to workmen in the refractories and sandstone industries. The exception here was that compulsory suspension applied to skilled workmen who had contracted the disease but who at the date of diagnosis had not been employed in the industry (there were minor qualifications) for more than 20 years *and* who had not reached the age of 40 years (sandstone) or 45 years (refractories). Both conditions had to be fulfilled simultaneously. The explanation is simple, namely, that such workmen were regarded as unduly susceptible to the risk and so likely to suffer inordinately from further exposure. As a rule all unskilled and semi-skilled workmen were liable to suspension and this included all workers in the asbestos industry. Permanent suspension, of course, remained as a condition of the receipt of compensation, which once accepted could not be surrendered. Suspension did not necessarily imply incapacity for work. The medical board could certify that the physical capacity of the workman was not impaired by the disease, in which circumstances compensation was restricted to a maximum period of 13 weeks.

The certificate of the medical board was final and conclusive of the matters therein certified : there was no appeal even to the courts except on points of law.

In all compensation claims and other cases involving suspension, as at periodical medical examination, *x*-ray examination was compulsory. Moreover both members of the Board were required to examine each workman and if not agreed they were further required to submit the case to the Chief Medical Officer for his decision. This was an advance on the procedure of the original Medical Board under the Refractories Industries (Silicosis) Scheme, 1925, in which the appointed senior member had a casting vote.

In practice the Scheme worked well and without substantial complaint. This does not signify that there was neither criticism nor opposition in individual cases but in the main the complaints related to legal considerations. They did, however, emphasize the narrow prescription of scheduled industries and processes and foreshadowed the need for further extension.

Although the Scheme was under the authority of the Home Office, the Government did not accept, apart from a small annual contribution, any financial responsibility for the costs of administration. The Scheme was intended to be self-supporting and towards this purpose a system of fees for the various services, some payable by employers, others by the workmen, was prescribed in the Silicosis and Asbestosis (Medical Fees) Regulations, 1931. The fees were paid into the

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Medical Expenses Fund, which was managed by the Home Office, and out of this fund all incidental expenses, including the salaries of the medical officers, were paid.

So after 25 years (1906–1931) of inquiry and experience certain principles and methods of administration had been established and in some measure enforced by legislation. The schemes made in 1931 were to continue, apart from minor extensions and amendments, according to pattern until 1943.

Amendments and Extensions

Certain operations in coal mines, it will be recalled, were included for the first time in the Various Industries (Silicosis) Scheme, 1928. The workmen covered, however, constituted a relatively small group, namely, men engaged in drilling and blasting in *silica rock*. This soon gave rise to difficulties of interpretation in individual cases and appeared to involve serious hardship, if not injustice, to many coal-face workers and other underground workers. Following certain decisions in the courts the immediate difficulty was resolved by the Various Industries (Silicosis) Amendment Scheme, 1934, whereby the Scheme was amended so as to apply to " any operation underground in any coal mine ". A similar amendment in 1935 added " Haematite Iron Ore Mines : any operation underground ", and then in 1939 " Slate Mines : any operation underground ".

This method of extension by adding narrowly prescribed occupational groups became a standard practice.

Byssinosis

Meanwhile the textile workers' unions in Lancashire had been carefully watching the trend of legislation because, for nearly a century, cotton card-room and blow-room workers had suffered inordinately from chronic respiratory disease. The disease was known as byssinosis and presented clinically as chronic bronchitis and emphysema, often very severe and disabling at or after middle life. Representation had frequently been made to have the disease added to the schedule of industrial diseases under the Workmens Compensation Act. The excessive incidence of the disease, in some measure, supported the view that it fulfilled the qualification to the third test of the Samuel Committee, namely, that : " in the case of a disease which is common in a particular trade and exists, though very rarely, outside the trade, it might be right to make that disease the subject of compensation " (Home Office, 1932).

The difficulty, however, was to distinguish the truly occupational cases from those due to other causes, especially as there existed no specific radiographic appearances, as in silicosis and asbestosis, by which the disease could be identified in individual cases. Ultimately a compromise solution was accepted and given effect in the Byssinosis (Workmen's Compensation) Scheme, 1941. Compensation was provided for cases in which a workman (*males only*—females were not included until 1948) established that " he had been employed for a period of or periods amounting in the aggregate to *not less than* 20 *years* in the employment, as defined, and where the Medical Board certified that the workman was *totally disabled* and *permanently incapacitated* for work as the result of the disease or that the death of the workman had been caused by the disease ".

The significant provisions are printed in italics.

The Scheme, which applied only to workmen employed on or after May 1, 1941, operated through an administrative board comparable to the joint committees under the early refractories and sandstone schemes, while the medical examinations were made by a specially appointed medical board. In this instance the number of cases did not justify the employment of full-time medical officers and so local consultant physicians with special experience of the disease were appointed for the purpose.

Supplementary to this compensation scheme an innovation appeared in the Byssinosis (Benefit) Scheme, 1941. This scheme applied to men who had ceased employment before May 1, 1941, and so were excluded from the compensation scheme. The medical and administrative arrangements were the same and the benefit for certified cases was a weekly payment of 10s.

Pneumoconiosis of Coal Miners

Generally the machinery worked well. However, there was one serious exception and that related to disabling respiratory disease in coal-miners. Claims among this group, particularly in South Wales, became increasingly numerous, but an unduly high proportion were rejected by the Medical Board on the grounds that the workman was not suffering either from silicosis or silicosis accompanied by tuberculosis. This notwithstanding the doctors recognized and directed the attention of the authorities to the fact that many of the miners, who presented for examination and failed to obtain a certificate under the Scheme, were disabled by chronic chest disease. Furthermore this disease was accompanied by radiographic changes—often extensive—in the lung, and were apparently of occupational origin as they did not occur in the general population of the area. These abnormal

appearances, however, did not conform to those normally regarded as indicative of silicosis. The situation was serious—increasingly so—and could not be ignored. Accordingly the Home Office and the Mines Department through the Medical Research Council undertook to arrange a comprehensive inquiry into the problem and, if necessary, to implement the findings by appropriate legislation. In 1936 Dr. P. D'Arcy Hart and Dr. E. A. Aslett assisted by other experts started an investigation in the South Wales coal-field. The actual field studies began in December, 1937, and were completed early in 1941. The findings were published in February, 1942, in a report entitled " Chronic Pulmonary Diseases in South Wales Coalminers ".

Dr. D'Arcy Hart and Dr. Aslett confirmed the occurrence and serious incidence of chronic respiratory disease among coal-miners throughout the area and occasionally among other workmen employed in handling coal, such as coal trimmers at the docks. The disease, which was attributed to the inhalation of mine dust, was characterized by abnormal radiographic appearances which could conveniently be classified into two main divisions, " consolidation " and " reticulation ".

For the purposes of the present review the following section on nomenclature is relevant :

> " Since reticulation is undoubtedly due to dust of some kind but cannot, at present, be termed a form of silicosis, and since consolidation itself shows certain characteristics post-mortem which are rather different from classical silicosis, it is suggested for simplicity of nomenclature that the changes represented both by reticulation and by consolidation be included under the term ' pneumokoniosis of coal-miners '. Alternatively, it is suggested that ' silicosis ' (or ' anthraco-silicosis ') continue to apply to the consolidation type of abnormality, and that the term ' dust-reticulation ' be introduced, leaving the latter's causation to be elucidated by further research. The first of these alternatives is preferred."

In effect the conclusion was that " pneumokoniosis of coal-miners " was not identical with silicosis and so not covered by existing compensation legislation.

The Report was accepted and as promised the Workmens Compensation Act, 1943, was passed to enable the Secretary of State to make schemes applying the Workmens Compensation Act to workmen suffering from *any form* of pneumoconiosis. For the purposes of the Act the expression " pneumoconiosis " was defined as " fibrosis of the lungs due to silica dust, asbestos dust or other dust, and includes the condition of the lungs known as dust reticulation ".

In pursuance of this power the Coal Mining Industry (Pneumoconiosis) Compensation Scheme, 1943, was made with effect from July 1, 1943, and applied to all underground workmen and certain surface workers in coal mines employed on or after this date. The Pneumoconiosis (Benefit) Scheme, 1943, made provision for a weekly payment of 15s. to workmen who had been employed in or about any coal mine after October 22, 1934, but not after June 30, 1943. This benefit, however, was limited to cases of total disablement or death by the disease.

It will be recalled that Hart and Aslett had recorded the occurrence of the same disease among coal trimmers employed at docks in the handling, moving, stowing, and packing of coal for transportation in ships. Owing to administrative difficulties it was not possible simultaneously to make a scheme for them but ultimately this was achieved in the Shipping Industry (Pneumoconiosis) Compensation Scheme, 1946.

The immediate effect of these schemes was an enormous increase in the number of claims by coal miners, not only in South Wales but throughout the country. Whereas new certified cases numbered 465 in 1939, by 1944 they had increased to 2,069 and reached a peak of 5,821 in 1945 (McVittie, 1949). The number of medical officers and centres was increased but not commensurately as doctors experienced in the work were not available. The result was that the work of the Medical Board became seriously disorganized and almost entirely restricted to the duties of adjudicating claims.

Several minor amendments and additions to the schemes continued to be made but these did not alter the main pattern, which by now was well defined. Compensation payments were adjusted to meet the higher cost of living ; initial examinations were restricted but without diminishing their purpose ; periodical medical examinations were extended to include female earthenware tile-pressers (hitherto the examinations were restricted to male tile-operatives) in the pottery industry. Following the observations of Davies (1939) among slate miners these workmen were enabled to obtain compensation but splitters and dressers were not added to the list of scheduled processes until 1946.

Meanwhile, on the basis of the Beveridge Report (Interdepartmental Committee on Social Insurance, 1942), the advent of the new comprehensive health insurance scheme including industrial injuries was imminent. This when enacted was to introduce radical changes in the principles and administration of workmen's compensation.

The National Insurance (Industrial Injuries) Act, 1946

This Act came into force on July 5, 1948, and applied to all workmen employed on or after that

date : other workmen remained covered in accordance with the Workmens Compensation Act and schemes made thereunder. As these involved a time limitation—usually five years or less—they would ultimately become defunct.

The first important change was that employers, save for existing and transitional liabilities, ceased to bear compensation payments, which became the responsibility of the State through the Minister of National Insurance and the Industrial Injuries Fund. This fund is maintained by compulsory weekly contributions from all insured persons and their employers. Thus for the first time the workman made a direct contribution, it was in fact an insurance scheme in which payment of contributions entitled the injured workman to prescribed benefits and allowances, which were *additional to* and on a higher scale than normal sickness benefits under the Health Service.

Formerly compensation payments were based not on injury but on actual loss of earnings and then subject to a maximum amount. Now disablement benefits were assessable on a percentage basis related to a prescribed flat rate and without regard to the level of individual pre-accident or post-accident earnings. Additional reliefs, however, were provided, where applicable, in the form of special hardship and constant attendance allowances and unemployability supplement. The benefits accrued as weekly payments, even if the workman continued at work, and could not be commuted for lump sum settlements. Another important change was that receipt of industrial injury benefits did not preclude a workman subsequently from obtaining damages at Common Law. Indeed in some industries, notably iron and steel, such actions have become a routine procedure and many cases have gained very substantial awards either in the courts or by agreement.

The most radical change was in the assessment of disablement in which the criterion was not simply the intrinsic handicap arising from the injury or disease but the loss of physical and mental faculty—loss of health, strength, or the power to enjoy life—as measured by comparison with a person of similar age and status. In addition due regard, by suitable weighting of the award, was given to the interaction of the injury with concomitant but extraneous disease. For example, in pneumoconiosis the injury to the lungs may lead to loss of faculty through shortness of breath, and other symptoms. This imposes disabilities at work or play, as, for example, restriction of capacity for and speed of work, inability to climb stairs or to walk quickly. The sum of these disabilities makes up the disablement resulting from the disease, and this may be aggravated in individual cases by concomitant though unrelated disease of the heart or other organs and systems.

Actual assessments were made on a percentage basis in steps of 10%.

The National Insurance (Industrial Injuries) (Prescribed Diseases) Regulations, 1948

The Act having provided the general framework, the detailed provisions were dealt with by regulations. Under the Prescribed Diseases Regulations " pneumoconiosis " was defined as " fibrosis of the lungs due to silica dust, asbestos dust or other dust, and includes the condition of the lungs known as dust reticulation but does not include byssinosis ".

The emphasis on fibrosis as an essential characteristic (since confirmed by the Industrial Injuries Advisory Council, 1953) is significant as thereby all non-fibrotic forms of dust disease of the lungs, such as siderosis of welders and poisoning by beryllium, were excluded. Byssinosis likewise did not conform to this definition but had already been accepted and so was dealt with separately in subsection (2) of section 57 of the Act, which provided disablement benefit where the claimant was certified to be totally and permanently incapacitated for work by the disease. This was later amended under the Prescribed Diseases Regulations so that benefit became payable where the loss of faculty was likely to be permanent and assessed at not less than 50%.

As established under previous schemes where a person was found to be suffering from pneumoconiosis and tuberculosis the effects of the tuberculosis were treated as if they were the effects of the pneumoconiosis.

Despite the insurance character of the Act the right to disablement benefits and allowances under the Regulations was not made universal to all workmen but continued to be restricted to scheduled occupations and processes. Opportunity, however, was taken to extend the number of these occupations and processes and later others, for example, certain carbon workers and boiler scalers, were added. The Trades Union Congress continued to direct attention to cases of hardship resulting from this narrow prescription and pressed for a more general approach. The Minister of National Insurance ultimately referred the matter to the Industrial Injuries Advisory Council. It was recognized that " open " prescription would assist the workman but would probably result in a spate of claims, many of them frivolous. In their Report (1953) the Council recorded that the present schedule, built up as the result of many years' experience, did in fact cover the

occupations of the great majority of workers exposed to a risk of pneumoconiosis. For this reason they supported the existing system. They did, however, recognize that " sporadic " cases did arise from unscheduled occupations and so they recommended that such cases should have access to the pneumoconiosis medical panels on submission of satisfactory evidence that the nature of their employment and the nature of their illness constituted reasonable cause to suspect that they were suffering from pneumoconiosis.

Medical Arrangements

The Regulations made provision for setting up panels of specially qualified practitioners at various centres throughout the country. From these panels medical boards of two or more doctors could be formed to deal with pneumoconiosis and byssinosis cases. This was achieved by transferring the medical officers of the existing Medical Board from the Ministry of Labour and National Service to the Ministry of National Insurance. Dr. C. L. Sutherland, the chief medical officer, was appointed to the headquarters staff of the Ministry in London. As a result the separate panels became, except for a measure of joint consultation, almost autonomous and without a chief medical officer to coordinate the work and maintain standards.

Formerly the certificate of the Medical Board was final. This provision was maintained save that after the expiry of two years from the date of first certification an aggrieved workman could appeal to a special Medical Appeal Tribunal, but only against the disablement assessment ; there was no appeal on the grounds of diagnosis.

The arrangements for initial and periodical medical examinations were continued as before but the interval between examinations was fixed, irrespective of the degree of risk, uniformly at two years.

Present policy seems directed to abolishing full-time medical officers, a system which had proved its value over years of trial and experience. This is revealed by the fact that full-time medical officers who leave for any reason are not being replaced. Local chest consultants and others are being employed part-time to constitute medical boards. While experienced in chest diseases, few of these physicians have any wide practical experience of the pneumoconioses or of the causative occupations and processes. Nor do they assist in periodical medical examinations or post-mortem examinations, an essential part of the training of experts.

The origin of this situation may be traced to the Committee on the Pay and Organization of Civil Service Medical Staffs under the chairmanship of Sir Harold Howitt, which presented a report in April, 1951.

> " It seems to us that the work of the Pneumoconiosis Medical Panels is too narrow and routine to provide a satisfying job for a doctor throughout his working life ; nor, as it is at present organised, can it provide adequate career prospects. Moreover, and what is more important, there is in our view nothing in the nature of the work which requires that it should be undertaken by doctors limiting themselves to one condition such as this ; on the contrary, we consider that advantage would accrue both to the individuals affected and to the doctors concerned if the work were done in the Chest Clinics of the National Health Service. We recommend that the work be transferred to the National Health Service."

It is almost impossible to oppose this statement simply because of the qualification " the work . . . as at present organised ". This notwithstanding it excites thought on what a physician seeks in the practice of his profession. To some this narrow field would seem to provide the ideal experience : to observe men in health, disease, disablement, and death : to engage in clinical work in health, through the progress of a disease and face the ultimate test of the necropsy : to study pathology and histology : to observe men at work in factories and mines : to study the socio-economic effects of disease in the community : to combine law and medicine, and learn by contact something of the outlook of employers and trade unionists. Finally to observe and record—which, after all, is the essence of research.

In the interval there has been only one faint official counter to this policy. It occurs in the Report on Pneumoconiosis by the Industrial Injuries Advisory Council, Ministry of National Insurance (1953).

> " We wish to mention here that we attach considerable importance to maintaining the calibre and standing of the Pneumoconiosis Medical Panels and that it seems to us highly desirable that the Panels should continue to include at least a nucleus of experienced full-time members, as at present. Apart from other advantages, this would in any case seem to be necessary in order to ensure uniformity of practice in matters of diagnosis and assessment."

Pulmonary Disability

Increasingly over the past few years representations have been made that, in certain industries, notably coal mining and iron and steel foundries, bronchitis and emphysema should be recognized as occupational diseases. South Africa has again given the lead in the Silicosis Amendment Act, 1952, Union of South Africa, which provides compensation benefits in respect of " pulmonary disability " which is defined thus :

" Pulmonary disability means an impairment of the cardio-respiratory functions of a person which in the opinion of the Bureau : (*a*) has substantially and permanently diminished the capacity for work of the person in question ; and (*b*) resulted from the performance, by the person in question, of work in a dusty occupation."

It is unlikely that this problem can much longer be ignored in Great Britain. Probably it will be the subject of evidence and discussion in the Departmental Committee which was set up by the Ministry of National Insurance in July, 1953, " To Review the Diseases Provisions of the Industrial Injuries Act."

Moreover, byssinosis, which has been compensatable since 1941, conforms to this definition of pulmonary disability.

Conclusion

So it emerges that after nearly 50 years dust diseases of the lungs, on an ever-widening but not yet comprehensive front, have been accepted as industrial diseases, while compensation, in the form of benefits and allowances, has been provided almost universally for patients and their dependants. More accurate diagnosis has been achieved by advances in chest radiology and through better knowledge of the pathology of the various pneumoconioses.

In the course of this review many names have been cited but, paradoxically, three of the greatest authorities have not been mentioned. I wish to pay tribute to the outstanding contributions of Sir R. Bannatyne, C.B., and E. Field, Esq., C.B.E., formerly of the Home Office, and Dr. E. L. Middleton, O.B.E., sometime one of H.M. Medical Inspectors of Factories. And none rendered greater service than Dr. C. L. Sutherland, C.B.E.

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TUMOURS OF THE URINARY BLADDER IN WORKMEN ENGAGED IN THE MANUFACTURE AND USE OF CERTAIN DYESTUFF INTERMEDIATES IN THE BRITISH CHEMICAL INDUSTRY*

PART II. FURTHER CONSIDERATION OF THE ROLE OF ANILINE AND OF THE MANUFACTURE OF AURAMINE AND MAGENTA (FUCHSINE) AS POSSIBLE CAUSATIVE AGENTS

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In a previous communication (Part I) on occupational bladder tumours (Case, Hosker, McDonald, and Pearson, 1954), the primary object was to consider the statistical evidence which had been collected about the manufacture and use of the dyestuff intermediates aniline, benzidine, α-naphthylamine, and β-naphthylamine, and their relation to occupational tumours of the urinary bladder. It was concluded that aniline manufacture and use were probably not a cause of the disease, but that certain aniline workers who were employed in the manufacture of magenta (fuchsine) might be in some danger of developing occupational bladder tumours. At the same time it was suggested that the manufacture of auramine might also be a source of danger, and arrangements were made for a more detailed investigation of the occurrence of bladder tumours in workmen exposed to the manufacture of magenta, in which process aniline is necessarily used, and the manufacture of auramine, where aniline is not used.

This investigation, being part of the A.B.C.M. Papilloma Research Scheme (Association of British Chemical Manufacturers, 1953), was of necessity confined to the same firms as had hitherto been investigated and the data relate only to the manufacture of magenta and auramine. These substances differ from the other substances so far studied in that they are finished dyes, and will be used by a different industry from that being investigated. Thus the conclusions to be drawn from the results presented below do not mean that the finished products magenta and auramine are necessarily causal agents; the data in this study do not enable this point to be elucidated. No investigation of the industry using these substances has been made.

This paper is intended to be complementary to Part I. The limitations of the statistical analysis discussed therein remain valid, the sources of information are the same, and any special terms previously defined are used with the same meaning.

Historical

It is perhaps a fruitless speculation to attempt to assess the true aetiological role of aniline in the cases attributed to this substance in the earlier literature, since frequently no clear distinction was made between aniline contacts and magenta contacts, and a review of the literature on impurities in industrial aniline used in earlier times (Walpole, Williams, and Roberts, 1952) reported the presence of α- and β-naphthylamine and 4-aminodiphenyl in the material. Subsequently 4-aminodiphenyl has been shown to produce bladder tumours in dogs following the oral administration of the material (Walpole and others, 1954). A list of cases attributed by various authors to aniline was given by Berenblum in 1932 and in a publication from the International Labour Office in 1921, and reviewed

* Part of the cost of publishing these papers was defrayed by the Association of British Chemical Manufacturers and the Chester Beatty Research Institute.

more recently by Hueper (1938). The following work relates only to industrial experience with aniline, magenta, or auramine between 1910 and 1952 in the firms investigated in the British chemical industry.

Data, Methods, and Results

Nominal rolls of men engaged in the manufacture of auramine and magenta were supplied by Group I* firms who had contributed nominal rolls to the original investigation. A careful cross-check was made to eliminate men who were recorded as also having had contact with benzidine, α- or β-naphthylamine. As before, men who had started work before 1910 with the firm submitting the nominal roll were rejected. As will be seen later, two men who subsequently developed bladder tumour were properly placed on the nominal roll since they started work with the firm after 1910, but the investigation of their history showed that they had previous experience elsewhere with auramine and magenta manufacture, though no contact with the naphthylamines or benzidine. They were therefore allowed to remain on the nominal roll, but the extra experience was added to the induction and exposure times. One case of a bladder tumour was encountered where the lapse of time from first starting work in the manufacture of auramine to developing a tumour was three months. By definition this man did not meet the minimum requirement of six months' employment in the industry to be included on the nominal roll, and, since some might argue that it is highly unlikely that such a tumour was occupational, it has been thought advisable to omit the case from all the statistical procedures. This does not mean that the authors absolutely reject the possibility that the case was in fact occupational.

After the nominal rolls submitted had been scrutinized in this way, it was possible to divide them into the following exposure classes: (a) those men who had had contact with aniline but not with magenta, auramine, benzidine, α- or β-naphthylamine. The contact might have been in manufacture or use; (b) those men who had manufactured magenta, but who had not come into contact with auramine, benzidine, α- or β-naphthylamine; (c) those men who had manufactured auramine, but who had not manufactured magenta or come into contact with benzidine, α- or β-naphthylamine; (d) a small group of men who had manufactured both auramine and magenta, but who had not come into contact with benzidine, α- or β-naphthylamine.

The nominal roll for each exposure class was then set out as described in Part I and the expected number of death certificates at the mean rate for males in England and Wales computed by the comparative composite cohort analysis method described by Case (1953a, b) and employed in Part I. This calculation was made to include experience to the end of 1952, a later date than that used in Part I. In the new nominal rolls for magenta and auramine workers there was no class of men with incomplete data, although in the estimate for aniline workers

* Those firms taking part in the investigation which manufacture aniline, benzidine, α-naphthylamine or β-naphthylamine (see Part I).

TABLE I

NO. OF DEATH CERTIFICATES EXPECTED IF NO SPECIAL RISK WERE OPERATING AND THE NO. OF CASES AND DEATH CERTIFICATES FOUND FOR VARIOUS EXPOSURE CLASSES

Rank	Class	Group*	Total No. of Cases Found	Cases on Nominal Roll			Cases on Nominal Roll where Death Certificate Mentions Bladder Tumour	Expected No. of Such Cases	No. of Men on Nominal Roll	Significance of Difference	P
				Total	Alive	Dead					
1	Aniline without benzidine, naphthylamine, magenta or auramine contact	I	3	3	2	1	1	0·52	812	None	>0·1
		II	0	0	0	0	0	0·30	394	None	>0·1
		III	0	0	0	0	0	0·01	17	None	>0·1
		All	3	3	2	1	1	0·83	1223	None	>0·1
2	Magenta contact	I	6	5	2	3	3	0·13	85	Very high	<0·005
3	Auramine contact	I	9	8	2	6	6	0·45	238	Very high	<0·005
4	Both magenta and auramine contact	I	1	1	1	0	0	0·02	9	None	>0·1
5	Either auramine or magenta contact (total of ranks 2, 3 and 4)	I	16	14	5	9	9	0·60	332	Very high	<0·005

*Group I, those firms which manufacture any one or more of the following substances: aniline, benzidine, α-naphthylamine, or β-naphthylamine; Group II, those firms which use but do not manufacture any of these substances, excluding those firms whose usage is confined to the purification of the substances for sale as fine chemicals; Group III, those firms which only purify any of these substances.

the proportion derived from incomplete data remains as shown in Part I, Table 2.

The nominal rolls were also checked against available hospital records and the alphabetical list of death certificates for bladder tumour discussed in Part I and by Case (1953a, b). The number of verified cases found and the expectation of cases if no unusual risk was operating are shown in Table 1. The nominal rolls are not set out in full, but the total number of men on them is shown.

It is concluded from Table 1 that there is no evidence whatsoever to suggest that the manufacture or use of aniline, under the conditions pertaining in the British chemical industry between 1910 and 1952, has been a cause of occupational bladder tumour.

It is also concluded that, despite the small groups available for study, there is good statistical evidence to suggest that the manufacture of both auramine and magenta carries with it an occupational hazard of contracting bladder tumour. This does not mean that the finished products, auramine and magenta, are the causal agents, and this analysis cannot help to elucidate this point.

The details of the cases found amongst the magenta and auramine cases are shown in Table 2.

In Part I it was shown that both the age at death and the age at onset were earlier in the occupational cases than in the general population and it was suggested that this could be a useful criterion of an environmental hazard. The present series of magenta and auramine cases is too small to be examined class by class but when amalgamated can be analysed.

The most precise method available for estimating the distribution of the ages at death that would be expected if it were similar to that in the general population is to use the partial sums of the composite cohort analysis calculation already made for Table 1 (see statistical appendix). This has accordingly been done, and a 2 × 2 contingency table drawn up to show the observed and expected deaths at ages of under 60 and 60 and over. This is shown in Table 3.

TABLE 2

DETAILS OF CASES OF BLADDER TUMOUR ONLY IN CONTACT WITH MAGENTA OR AURAMINE

Date of Onset	Age at Onset	Age at Death	Exposure Time in Years	Induction Time in Years	If on Nominal Roll	If Death Certificate Mentions Bladder Tumour	Class
1902	42	42	12	12	No	Yes	
1925	54	54	5	5	Yes	Yes	
1929	56	57	19*	28*	Yes	Yes	Magenta contact
1943	39	—	16	18	Yes	—	
1950	53	53	5	19	Yes	Yes	
1952	47	—	1	20	Yes	—	
1945	47	—	22	22	Yes	—	Both magenta and auramine contacts
1927	67	75	20*	20*	Yes	Yes	
1930	66	84	6	9	Yes	Yes	
1934	53	58	10	24	Yes	Yes	
1940	60	—	22	22	Yes	—	Auramine contact
1941	40	40	3	9	Yes	Yes	
1946	67	67	9	27	Yes	Yes	
1947	47	—	0·25†	0·25†	No	—	
1951	49	50	3	27	Yes	Yes	
1952	52	—	2	28	Yes	—	

*These two men were first employed by the member firm after 1910, and are thus properly included in the nominal roll. Both men had additional previous exposure to the relevant substance only and this additional time has been added in.

†This case is excluded from all statistical procedures.

TABLE 3

AGE AT DEATH AND AGE AT ONSET COMPARED WITH ESTIMATES MADE FROM SAMPLES OF THE GENERAL POPULATION

Age at Death	Under 60 Years	Over 60 Years	Total		Test of Significance
Nominal roll cases with bladder tumour death certificates only	6	3	9	Found	χ_c = 2·68
	2·1	6·9	9	Expected*	m = 2·1
					p = 0·23
					P = 0·007
Age at onset	**Under 50 Years**	**50–64 Years**	**Total**		
	10	3	13	Found	χ_c = 3·95
	3·3	9·7	13	Expected	m = 3·3
					p = 0·25
					P < 0·005

* The source of the line " expected " is discussed in the text.

Analysis by Fisher's exact test, using the χ_c technique (Fisher and Yates, 1948, Table VIII), shows the shift in the age at death towards the younger ages to be statistically significant.

The expected age at onset cannot be evaluated in this way, since no tables of morbidity data exist. The best means available to form the required estimate is to use the data relating to Birmingham hospitals used in Part I, limiting the upper age to 65 to avoid retirement bias, and to use all observed cases, whether derived from the nominal roll or not. A 2×2 contingency table on this basis also appears in Table 3, showing the observed and expected cases with an onset before the age of 50 and at 50 and over. (These lower figures are selected because of the

survival time from onset to death.) A χ_c analysis shows the lower age of onset to be statistically highly significant. It must therefore be concluded that the age at both onset and death in the occupational tumours of the bladder is lower than in the non-occupational cases.

The mean induction time of the 15 cases in the magenta and auramine classes shown in Table 2 (one of the 16 in the table is excluded) is 19·3 years with a standard deviation of 7·6 years. This does not differ significantly from the mean induction time (17·7, S.D. 7·2 years) found for the pooled data for benzidine, α- and β-naphthylamine cases discussed in Part I.

Summary

New nominal rolls of men exposed to the manufacture of magenta (fuchsine) and auramine have been prepared, and the previous aniline nominal roll has been revised by the removal of men exposed to the manufacture of magenta or auramine. It has therefore been possible to reconsider the evidence relating to the risks of contracting occupational tumour of the bladder in workmen engaged in these processes.

No statistical evidence has been found to suggest that the manufacture or use of aniline in the British chemical industry between 1910 and 1952 has caused occupational tumours of the bladder. This analysis is not necessarily relevant to the observations of other authors in other countries or in earlier times on cases attributed to aniline.

The manufacture of auramine or magenta in the British chemical industry between the same dates appears to have a definite occupational hazard of causing tumour of the urinary bladder attached to it, a statistically significant excess in the number of deaths certified as being due to bladder tumour being found, and the age of onset and death from the disease in the cases found amongst these manufactures being earlier than in the general population.

This statistical analysis is not capable of determining the causal factor in this risk attached to the manufacture of magenta and auramine, and it should not be assumed that the finished products are necessarily dangerous. No studies on the use of the finished products have, however, been made.

We should again like to thank those firms which undertook the laborious task of compiling the nominal rolls, and also Professor F. Grundy for certain criticisms that led to the use of the partial sum of the composite cohort analysis being used to estimate the expected age distribution.

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STATISTICAL APPENDIX

A METHOD OF CALCULATING THE AGE-DISTRIBUTION OF DEATHS OCCURRING AT THE DISTRIBUTION EXPECTED FROM THE GENERAL POPULATION BY THE PARTIAL SUMS OF THE COMPOSITE COHORT ANALYSIS

In both Part I and Part II of this work the method of obtaining an estimate of the expected age-distribution of deaths from bladder tumour by a partial summation of the composite cohort analysis (Case, 1953b) sum is mentioned. It seems convenient to explain this procedure in more detail as an appendix, but reference to the tables given in "The Expected Frequency of Bladder Tumours in Works Populations" (Case, 1953b) is essential to an understanding of this exposition.

If we consider Table 2 of that paper we find the number of men of a defined age group Z set out in accordance with the time when they started work. They are then observed for a period of years defined as X until the date of "assessment", and an estimate of the total number of death certificates expected is found for that particular group of people from the product column ($n \times a \times b$) divided by 10,000. If, instead, we subdivide the period X into a series of convenient periods, X_1, X_2, X_3, etc., each of which now has a new mid-point, the original estimate $n \times a \times b \div 10{,}000$ can be regarded as the sum of the estimates for the period X_1, X_2, X_3, . . . etc., but each such estimate will refer to a different age group, viz., Z_1, Z_2, Z_3, . . . etc. This procedure is then employed throughout the whole calculation, and the contribution of each Z_1, Z_2, Z_3, . . . etc., summated separately. From the grand total and these sub-totals, the proportionate distribution to each age group can be calculated. Computing may be minimized by considering the number of classes of Z that will be necessary ; e.g., in Part I (Table 2a) the number of observed cases available allowed the use of four such classes, whereas in Part II (Table 3) only two could be used.

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THERMAL CONDITIONS IN WARSHIPS REFITTING AT H.M. NAVAL BASE, SINGAPORE

BY

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From the Royal Navy

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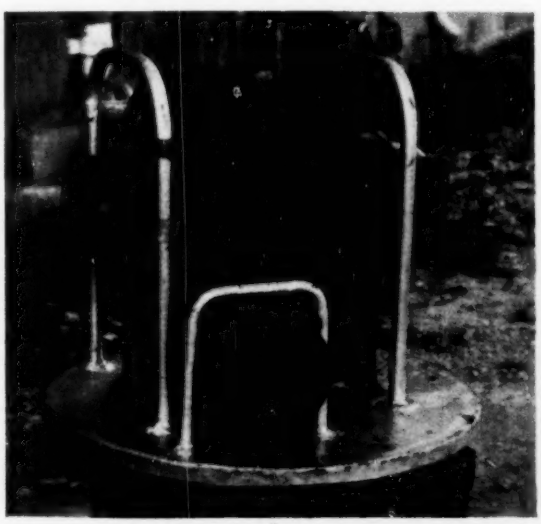
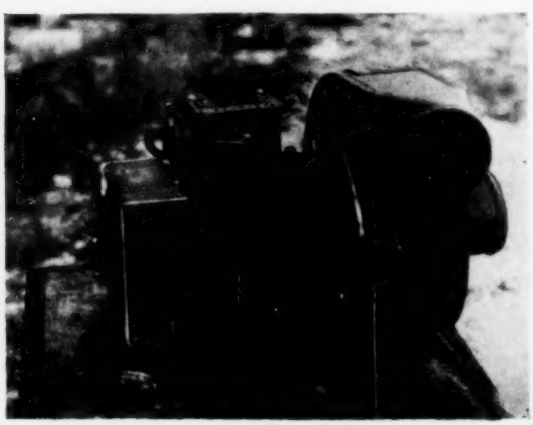
Numerous investigations have been carried out in recent years to determine the thermal environment in warships at sea in the tropics. As far as is known there has been no previous study of the thermal environment in which men work when a ship is refitting in a dockyard in the tropics. The aim of this investigation was to assess these conditions by measuring air temperatures in a wide variety of compartments in different classes of ships during a refit, and to relate the findings to the levels of warmth above which it is known that increasing numbers of men are likely to collapse or become inefficient.

Temperature recordings were made during July, August, and September, 1951, in an aircraft carrier repair ship, two cruisers, a frigate, and a submarine. They were in dry dock, except on one occasion when the ship was alongside. Thirty-five compartments in all were investigated. An important part of the work was to estimate the effect on the thermal environment of artificial ventilation or recirculation of air.

For the larger ships a refit usually lasts about eight to 10 weeks, of which five to seven weeks are spent in dry dock ; for submarines a refit takes much longer. The conditions in a ship during a refit are abnormal, but vary slightly from ship to ship. While in dry dock, boilers are shut down and machinery is not running. As a result there is much less " wild heat " circulating within the ship than under normal conditions, but as power is not available there is usually no forced ventilation supply or exhaust. Dockside power is used for lighting and the recirculation of air between decks. On occasions a forced fresh air supply can be delivered through the punka louvre system to certain parts of the ship, but in many compartments the only method of circulating the air is by means of " double-bottom " fans, *i.e.*, fans with hose extensions normally used to ventilate the space between the outer and inner plates below the water line (Fig. 1). As it is frequently not possible to arrange the intake from the outside air, the main effect is to increase



A



B

FIG. 1.—A is a 10-in. fan supplied with a 12-ft. length of canvas hose, and B a 5-in. fan supplied with an 8-ft. and 16-ft. length of canvas hose, showing air intake and outlet openings to which hoses can be attached.

the air movement within the ship without supplying fresh air.

Ships' staffs are employed as well as Asian dockyard workmen. A modified tropical routine is adopted for some of the ship's staff, especially the engineering and electrical branches. The working hours were five a day although the actual times varied from ship to ship. In submarines, only Asian workmen are usually employed on manual work, with the ship's staff supervising. The men work stripped to the waist or wear overalls. The work is sometimes heavy and occasionally very unpleasant, as for example when water tanks are painted with bituminous compounds, when oil fuel tanks are cleaned, during welding processes when fumes may be strong, or in lagging operations when the atmosphere is dusty. All ships' companies are accommodated ashore during a refit.

Methods

The 35 compartments selected for this survey were nearly all between decks with no natural ventilation from the outside air, where conditions might be expected to be severe.

The methods for measuring environmental warmth were those described by Bedford (1946). External air temperatures were taken on the upper deck in the shade on each day before temperature measurements were made in compartments.

Dry-bulb, wet-bulb, and globe thermometer temperatures were observed in every compartment investigated. High temperature silvered kata thermometers (cooling range 130° to 125° F.) were used to measure the air speed. Effective temperatures were calculated from these observations. Observations were made in some compartments when double-bottom fans were in use, and in one small compartment when a table fan was used.

Results

The dry- and wet-bulb temperatures observed in the various compartments when the external temperatures ranged from 80° to 92° F. dry-bulb and 74° to 81° F. wet-bulb are summarized below :

Dry-bulb Temperature		Wet-bulb Temperature	
Range (° F.)	No. of Observations	Range (° F.)	No. of Observations
84–87	9	80–83	18
87–90	13	83–86	11
90–93	4 9	86–89	4
93–96	2	89–92	1
96–97	2	92–93	1

Most of the dry-bulb temperatures lay below 93° F. and most of the wet-bulb temperatures below 86° F.

Globe thermometer temperatures differed on only two occasions by more than 2° F. from the dry-bulb temperatures recorded, namley, in a provision store and in one of the gun turrets on the upper deck, which was exposed directly to the sun's rays, showing that in this situation radiant heat may be a more important factor to consider. In the other compartments, which were between decks, radiant heat was not important.

Normally the air movement in the unventilated compartments was "still" (less than 10 feet per minute). When "double-bottom" fans were rigged, the air movement, but not the fresh air replenishment, was good, but then only when measurements were made in the direct line of the air flow from the fan. The air intake to the fan was usually from the compartment itself or an adjacent compartment, and so the fan merely recirculated air of the same temperature as the compartment air, and aided cooling of the body by increasing air movement. In only one of the 17 compartments investigated between decks was it possible to feed the fan from the outside fresh air.

Effective temperatures, calculated from basic and normal scales (as some men worked stripped to the waist and others wore overalls), were fairly high when there was no air movement, ranging from 81° to 93° F.; the majority lay between 84° and 87° F.

Effective temperatures were lowered appreciably when fans were working and the air stream was directed on to the recording instrument. On these occasions the level of the basic effective temperature (for men stripped to the waist) was on the average 2° F. below the corresponding normal effective temperature. Only a small distance from the line of the air stream, however, the air speed was very low.

Discussion

Although there have been many investigations in the past 50 years to determine the upper endurable limits of warmth for living and working conditions, it has not been possible as yet to state precisely under what conditions health will suffer, or to lay down exactly the acceptable environment for persons living and working in the tropics.

In the present investigation measurements were made only in compartments where the more severe conditions were likely to be encountered. No attempt was made to observe if any ill effects were experienced by the men, or if there was any lowering of their performance. The readings recorded will be discussed in the light of observations by other workers, who in the past have assessed the effects of hot environments on ability to work, efficiency, health, and comfort.

Ability to Work.—Haldane (1905), from investigations in a mine and laboratories in Britain, believed that at 85° F. wet-bulb temperature hard work was virtually impossible. Caplan and Lindsay (1946), however, investigating conditions in the Kolar gold fields in India, found that efficiency was hardly affected at this temperature. Caplan (1950) believes that 90° F. is the crucial wet-bulb temperature at which temperature conditions become oppressive, fatigue is more marked, and the fall in efficiency is about 40%. Above this temperature the danger of heat collapse increases. At a wet-bulb temperature of 93° F. after the third hour of exposure, little useful work could be done and latent or obvious signs of heat collapse were likely to be observed. These conclusions, however, were based on southern Indian workmen acclimatized to working at wet-bulb temperatures of 93° F.

Eichna, Ashe, Bean, and Shelley (1945), working at the Armoured Medical Research Laboratory, Fort Knox, Kentucky, give the following limiting wet-bulb temperatures in relation to performance for men working in an air movement of about 200 feet per minute.

	Relatively Easy	Difficult	Impossible
Completely saturated environment ..	92·5° F.	94° F.	96° F.

Thus there is a considerable difference between the definitions accepted by various workers for the limiting wet-bulb temperatures for different working conditions, but the range, 80° to 93° F., observed in compartments of ships refitting, when there was no air movement and with a high relative humidity, indicates that often the upper limits of tolerance were approached. The investigators, though only employed in the light activity of taking temperature readings over a short period of time, were drenched with sweat and found the conditions to be uncomfortable and exhausting.

The "effective temperature" is still recognized as the best available single index of the combined effects of air temperature, humidity, and air movement on sensations of individual comfort, though it may be misleading at very high levels of warmth. Yaglou (1926) found that the limiting conditions to which men could be exposed without sustaining ill effects lay between effective temperatures of 90° F. at rest and 80° F. doing heavy work; above 75° F. he found that the output decreased gradually until 80° F. was reached, when the fall was rapid. Bedford and Warner (1931) showed that the relative output of men filling tubs in coal mines in Britain was nearly halved when the average effective temperature was raised from 65·8° to 81·8° F. This finding can be compared with that of Caplan and Lindsay (1946) in the Kolar gold mines where efficiency remained at 100% when the effective temperature was 81·8° F.

It may be said, therefore, that under resting conditions men can tolerate an effective temperature of 90° F. for several hours without serious ill effects, but if work is done this temperature threshold is quickly lowered.

Efficiency.—Houghten, Stacey, Urdahl, and Watt (1942) investigated the effects of warm conditions on the skill of unacclimatized young men and found that there was no adverse effect when the effective temperature was 73° or 80° F. but that it was reduced when it was raised to 87° F. Mackworth (1945, 1946, 1947) found that the critical level, during which skilled work is not so accurate for acclimatized men dressed in shorts, lay between effective temperatures of 83° and 87·5° F., but, as Ellis (1950) points out, these figures seem to refer to the normal effective temperature chart and not to the basic chart for men stripped to the waist, which would put the zone at a rather lower level. Mackworth's experiments actually showed that the critical region, above which men will not work so efficiently, whether work is mental or physical, lies between effective temperatures of 81° and 86° F.

Comfort.—Investigations recently undertaken from the Royal Naval Tropical Research Unit, Singapore, indicate that there is optimum comfort for men living in warships in the tropics and engaged in sedentary occupations when the effective temperature is between 73° and 74° F. The upper acceptable level of warmth under these conditions (when more than 80% of persons are reasonably comfortable, and less than 20% wet with perspiration) is an effective temperature of 78° F. (Ellis, 1952).

Refitting Conditions.—In the compartments investigated the dry- and wet-bulb temperatures were all in the higher zones. The dry-bulb temperatures ranged from 84° to 97° F., and the wet-bulb temperatures between 80° and 93° F. At these temperatures the relative humidity of the atmosphere was usually over 75%, and in a few instances approached 100%. During the period these temperatures were taken the outside air temperatures varied between 80° and 92° F. dry-bulb and 74° and 81° F. wet-bulb. It is generally considered that the wet-bulb is more important than the dry-bulb temperature in assessing the effect of

climate on man. These figures show the marked increase in the warmth of the internal air.

The effective temperatures observed lay at a fairly constant high level *when there was no air movement*, temperatures ranging from 81° to 93° F., the majority lying between 84° and 87° F.

In the light of the evidence referred to above it seems reasonable to conclude that the upper limits at which men can work efficiently are often approached in ships refitting in the tropics; the limiting conditions in which they are able to continue at hard work are reached at times, and the workers almost invariably experience thermal discomfort which is often severe. Working conditions during a refit, however, are often much worse than these bare figures indicate, because the work is arduous and unpleasant in other ways owing to fumes or dust. The average period in dry dock alone for larger ships is usually between six and seven weeks, with a total period of refit of about two months. Conditions are further aggravated when men have to work in overalls. In some ships the men can be said to be well acclimatized to a hot climate, but in others the only period for acclimatization to the hot, humid climate of Singapore is during the passage south from Japan.

Remedial Measures.—The beneficial effect of air movement on comfort and well-being in the higher zones of air temperature and when relative humidity is high is known to be of the utmost importance. Haldane (1905) found that in an air current of about 135 feet per minute, a wet-bulb temperature of about 85° F. could be borne without an abnormal rise of body temperature. Dunham, Holling, Ladell, McArdle, Scott, Thompson, and Weiner, (1946) found that the limiting wet-bulb temperatures could be raised 2° to 3° F. if the speed of air movement increased from 10 to 200 feet per minute in hot humid conditions, but the effect of still air is more severe than the effective temperature scales indicate, and they suggest that the benefit gained by raising the general level of air movement above 300 feet per minute is exaggerated by the scales. An increase in air velocity from "still" conditions to about 200 to 400 feet per minute, with a "local cooling" effect, is required to produce a fall in effective temperature of 2° to 3° F., but even a few degrees' difference in effective temperature at the higher levels will produce a marked effect on comfort.

In ships refitting power is not usually available to provide ventilation by the punka louvre system. Compartments at the bottom of a ship are not normally provided with artificial ventilation though there may sometimes be a forced exhaust; the only natural ventilation is by manholes, hatches, or doors to adjacent compartments. When men are working in these compartments the only means of air supply is usually by "double-bottom" fans driven by dockside power. In the lowest compartments it is not possible to provide hose extensions to the outside air, and so the air supply is merely recirculated air from adjacent compartments.

"Double-bottom" fans can be used either as supply or exhaust fans. Two sizes are normally used (10 in. and 5 in.), with speeds of 3,500 and 2,800 r.p.m. and weighing 110 lb. and 60 lb. respectively. There are numerous practical difficulties in rigging them to provide an air supply to remote compartments, and even with long hose extensions it is not always possible to reach some spaces. Adequate numbers of fans may not be available for one reason or another. Work may therefore have to be done in many compartments without any artificial air supply or air movement.

Summary

An investigation of the thermal environment of men working in the compartments of warships refitting at H.M. Naval Base, Singapore, was carried out during July, August, and September, 1951.

Thirty-five compartments in which conditions were expected to be severe were investigated in different classes of ships. These compartments, in most instances, had neither artificial nor natural ventilation.

When ships are refitting the only remedy for improving conditions is to recirculate the air in compartments between decks by means of "double-bottom" fans with hose extensions. It is rarely possible to arrange the air intake from the outside air.

When fans were not available working conditions were often found to be severe, with high wet-bulb temperatures and high effective temperatures. The efficiency of workers was then likely to be affected adversely, and in some compartments temperatures were in the zone where arduous work for prolonged periods is known to be impossible. The conditions were always uncomfortably warm. Working conditions are aggravated by the nature of the work which is often arduous and unpleasant and when men have to work in overalls.

Beneficial effects from increasing air movement, so reducing the effective temperature when a local cooling effect can be achieved, are suggested by the measurements made.

Radiant heat is not an important environmental

factor in compartments between decks under refitting conditions.

I am greatly indebted to Surgeon Commander F. P. Ellis, Royal Navy, Director of the Royal Naval Tropical Research Unit, Singapore, for his advice in the preparation of this paper, to Sick Berth Chief Petty Officer W. Austin, A.R.S.I., for his assistance in recording temperatures, and to the Medical Director General of the Royal Navy for permission to publish.

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MISCELLANEA

Some Personal Observations on Industrial Health in the United States of America

BRYAN HARVEY*

Any account of industrial health in the U.S.A. should start with Dr. Alice Hamilton.† The autobiography of this remarkable woman records not only the author's life-long devotion to the cause of the American industrial worker, but gives a picture of conditions in American industry which, when she first began her work, were a veritable jungle of ignorance, prejudice, and suspicion. But if Dr. Hamilton showed the way out of these unpromising conditions, it was perhaps the alteration in American compensation law which provided the driving force toward change.

Industrial health may have owed something in its early stages to the experience of other lands, but the pattern which has so recently emerged is wholly American. Receiving little but advice from the Federal Government it takes its inspiration from the State compensation laws. Since these vary from State to State so also does the provision for industrial health. Most States in addition enforce, through their health departments, minimum standards ; but these also vary.

Most characteristic is the stimulus which compensation law gave to private enterprise. The insurance companies carrying the new burdens of compensation for industrial disease enrolled the services of the engineer and the chemist to control the health hazards of industry. So too did individual firms. That these firms saw the new services as extensions of their plant maintenance departments rather than of their medical departments seems to have had profound effects on subsequent development. This outlook introduced industrial hygiene as a new profession and has resulted in a characteristically American approach to the problems of industrial health, not the least feature of which was at the beginning the separation of industrial hygiene and industrial medicine.

Industrial Hygiene

While industrial hygiene in its widest sense is common to all countries with an industrial civilization, in its narrow sense it is *par excellence* the American contribution to industrial health. In so far as it is definable at all it comprises the measurement and control of industrial toxic hazards—that measurement being mainly of atmospheric contaminants while control is largely the engineering control of airborne poisons. This is not, however, an exclusive definition since other conditions, for instance, lighting and noise, to an increasing extent fall within the range of industrial hygiene.

The industrial hygienist is therefore part chemist, part engineer, and part toxicologist, though of course the clinical field is closed to him. Even so it seems that the American medical profession is less exclusive on these issues than its British counterparts and more ready to accept as colleagues workers trained in other sciences.

There is a good deal of concentration on methods of air analysis in order to determine the amount of contaminants in the atmosphere. This side of the industrial hygienist's work is highly developed, and involves serious academic training. Hygienists are employed by Federal and State agencies as well as by insurance companies and private firms.

Most of the techniques are well known in this country ; their novelty lies chiefly in their widespread use, and their acceptance often without qualification as a measure of industrial conditions. Grab sampling into exhausted bottles or by means of aspirators, and integrated sampling over a period of time are widely used, and the necessary laboratory equipment and facilities for analysis are provided as a matter of course. The use of physical methods as opposed to chemical methods is also being developed, and research into this rather specialized field of instrumentation is actively pursued. As yet these methods are not widespread.

The development of regular air sampling and analysis has resulted in the determination of theoretically allowable maximum concentrations. The present list sponsored by the Conference of Governmental Industrial Hygienists was started in about 1940 and is now almost universally accepted. It is from time to time amended, almost always by reducing the allowable concentration formerly accepted as safe, and this in itself is a powerful argument for those who object to the system. The argument put forward in justification is that if contaminants are to be controlled mechanically there must be a *standard* of atmospheric cleanliness to work to, a tacit rejection of 100% purity. These arguments do not always find favour in English eyes though they would seem to derive considerable support from pure logic.

Some at least of this technique of air analysis has been forced upon the hygienist since in the United States there is nothing comparable to Section 47 of the British Factories Act, which allows the word

* Mr. Harvey, one of H.M. Inspectors of Factories in the British Factory Department, was awarded a Rockefeller Foundation Fellowship for graduate studies in the Harvard School of Public Health in order to study industrial health in the U.S.A., and this article represents impressions gained in the course of his American visit. Any views expressed are personal to Mr. Harvey and do not necessarily represent those of the Ministry of Labour and National Service.

† Hamilton, Alice, (1943). *Exploring the Dangerous Trades*. Little, Brown and Co., Boston.

" offensive " to be an acceptable reason for providing exhaust ventilation. In almost every case where supposed toxic risks are encountered investigators have to show either physically or chemically that the agent is present in the atmosphere being breathed by the workers and that it is toxic. While this to some extent is a limiting factor, it can also demonstrate on occasion the presence of toxic materials in the atmosphere which were hitherto unsuspected.

Accurate assessment of air contaminants, particularly where the presence of small concentrations of some of the newer industrial poisons can be demonstrated, does notably assist in controlling health hazards. The American experience with metallic poisons such as beryllium, which has not so far been matched in this country, is a good example of the advantages of developing accurate air sampling techniques.

Some of the standards of dust sampling and counting which are considered acceptable are by our methods unsatisfactory since the official ideas on dust concentrations in the United States are based upon sampling by means of the Greenburg-Smith impinger which, so far as recent investigations show, may allow much of the dust of respirable size to escape. While a variety of methods of counting dust so collected has been developed, many workers, including the U.S. Public Health Service, feel that the whole technique is unsatisfactory. One of the difficulties, however, in getting rid of it lies in its widespread acceptance and in the fact that concentrations of dust based upon these methods have been accepted throughout the country as standards. This is a further example of the shortcomings of officially accepted lists of maximum allowable concentrations, particularly if the methods of determining the concentrations are not above reproach.

Other methods of sampling are, however, used in the United States, though the thermal precipitator does not appear to gain much favour, chiefly, I believe, because of the time needed for sampling.

One interesting instrument, developed by Bausch and Lomb, is effectively an improved version of the Owens jet dust counter. It consists of a pump of known capacity, a series of 14 microscopic slides which can be rotated on a disc, and a dark field microscope complete with its own lighting unit. It will take 14 separate dust samples and the graticule within the microscope allows the samples to be counted accurately in a short space of time. The results may not be quite so good as those achieved with the thermal precipitator but by virtue of the dark field method small particles can be counted, and the method is so simple that any normal person should with a little training be able to take and count dust samples with acceptable accuracy.

The very nature of this approach, involving, as it does, considerable theoretical training in the techniques of air sampling, has led to a noticeable concentration on theory. This is not, probably, a monopoly of industrial hygiene. In all aspects of life in America a high place is accorded to the scientist, and the theoretical approach has great popular appeal which is stimulated by advertisements. The theoretical approach has many advantages but is not without defects, the chief being that it tends to discount the common sense solution to any problem solely because it is simple. It may even lead to the elaboration of common sense solutions in order to make them acceptable.

Some of this has been forced on the industrial hygienist by conditions in industry itself. There is a strong feeling against any action to improve conditions until the industrial hygienist can demonstrate by instruments the presence of poison in the atmosphere. This attitude has led to the development of more and more accurate and involved means of air analysis in an effort to be more convincing to management. There may be a tendency, as a result, to judge the worth of the industrial hygienist by his skill in handling instruments rather than by his broad appreciation of the dangers of industry. Air analysis itself, unsupported by general background knowledge, may well have special pitfalls, particularly if the safe limits for an atmospheric contaminant are small. Sometimes the amounts to be measured are minute in the extreme, and the difference between safety and danger may be outside the margin of error inherent in the method of analysis. At the other extreme demands for scientific proof may lead occasionally to the curious spectacle of an industrial hygienist taking air samples in a room impossible to see across because of the density of the dust cloud. Industrial hygienists do not enjoy this sort of thing but are forced into it to show measurable proof of their observations. As a whole, American industry has more appreciation for the hygienist who can say, for example, with real accuracy how much benzene there is in the air than for the man who declares that the best way to end benzene poisoning is to get rid of benzene.

It is particularly noticeable, both in the academic field and elsewhere that among the lines of defence proposed against industrial poisons, substitution was the last, whereas in this country it is the first. All concerned with this work are heavily indoctrinated with the view that the industrial hygienist should confine himself to industrial hygiene and not propose changes in the productive process itself. It is almost an admission of failure by the industrial hygienist if he is forced to seek a substitute for the dangerous material. In this respect American thinking is fundamentally opposed to British thinking and strangely at variance with its own views on industrial safety, where it is held that safety is a problem of production and can only be solved by means of the normal administrative machinery of production.

It would be a mistake because some features of the American picture are unusual to British eyes to discount the tremendous work which is being done to improve industrial conditions. When one measures the progress made in so few years the results are really startling. Much of this credit must go to the insurance companies which quickly taught industry that industrial hygiene would pay. But much also belongs to private industry with its capacity for rapid change. One result of the compensation laws has been to introduce

this new fully accepted profession to American life with adequate financial support and its own facilities for teaching and research. There is now a vast and ever growing body of theoretical and practical knowledge of industrial hygiene in a climate of sympathetic public opinion which accepts the control of industrial health hazards as a separate branch of the science of public health. Whatever its deficiencies may be it can hardly fail to make progress. Americans are conscious of many of the defects themselves. In particular the recent trouble experienced with beryllium has given rise to fears that American industry by its very nature can produce new hazards faster than industrial hygiene can provide protection for them. Beryllium poisoning was a disaster because it eluded all their efforts and they feel that the same thing can happen again. In fact, there is now apprehension about the increasing use of radioactive isotopes. Already a number of minor incidents involving their unauthorized removal by employees and the distribution of components containing radioactive material from one company to another without any warning of the dangers have occurred. The use of these materials grows every day, and while at the moment the public is aware of the dangers (some might say over aware), this is bound eventually to be offset by familiarity as the years go by. Even now there have been enough incidents to cause considerable anxiety.

In atmospheric control the theoretical approach in industrial hygiene has paid handsome dividends. Interesting developments both in the control of purely toxic hazards by exhaust ventilation and also in the wider field of general ventilation are evident.

Air conditioning, often originally installed in industrial undertakings for the sake of the product, is now being considered also for its effect on the comfort of the operative and his consequent improved output. It involves the complete control of temperature and humidity, including refrigeration, and is a development peculiarly American in its origin. In the United States it is only the far western seaboard which enjoys a temperate climate. The rest of the country is beset with extremes of temperature at either end of the scale and generally at both. It is an interesting speculation as to what effect this control of natural environment will have on Americans themselves. For it is becoming widespread to the extent that one can buy an air-conditioning unit for the living-room or bedroom from the corner drug store ; and air conditioning of large public buildings and offices is becoming universal.

The possibility of boosting output by improved physical conditions has not escaped the notice of American industry, and while air conditioning solely for this purpose is not common, one or two interesting developments were noted. For example, the air conditioning of a roller man's " pulpit " in a large steel works proved well worth while in relation to the importance of the work which the man was performing.

In the whole field of ventilation, and in particular in the design of exhaust plants, there is evidence of wide appreciation of the theoretical problems of design, and great skill and ingenuity are used to overcome them. In this respect the universities deserve praise for turning out graduate hygienists with a good theoretical background. Ventilation problems appear to be tackled with greater skill and knowledge than in this country. A particularly ingenious example of this was in the fresh air supply provided for a crane cab in a steel works where there was danger of carbon monoxide poisoning. In the same works polished aluminium sheets had been used with great success to keep out radiant heat in various parts of the works—including the bottom of all the crane cabs near furnaces.

Application of modern dust control by ventilation in foundries is also good, and here again examples of ingenuity backed by good theory were apparent in adapting the ventilation plant to the processes. Where industrial hygiene was taken seriously, quite remarkably high standards of atmospheric control were often achieved and in this respect we in this country have something to learn.

The hygienist is now developing interest in problems related to the comfort of the worker. This development has recently received a remarkable stimulus from the Compensation Acts in relation to noise. Several successful claims for loss of hearing due to occupation have been made leading to much investigation by insurance companies and Federal authorities. In particular it is thought desirable to find if a " maximum allowable concentration " of noise can be determined which will not result in loss of hearing. The Federal Public Health Service is engaged in a long-term investigation undertaken in the Federal prisons among other places. The problem of loss of hearing already sustained before employment is also of great interest to insurance companies since some have already had to pay compensation for industrial injuries to former naval gunners. The tightening up of pre-employment examinations to include an audiogram is one result.

The social and economic climate in the U.S.A. is particularly favourable to research both because the capital resources are readily available, and also because scientific research is considered almost as part of the American way of life. It is possible to be over critical and say that some money is spent on projects which hardly merit it, but this may well be a small price to pay for the valuable information which is being gathered over the years in a comparatively new subject. Studies are going on in widely diverse fields. They range from the estimation of the effects of the absorption of minimal quantities of lead over long periods to investigations of the hazards of the industrially important rarer metals and of the cause of industrial cancer. The last two projects are under the aegis of the United States Public Health Service.

The Atomic Energy Commission sponsors both physiological research into the effects of radiation and also research into the problems of ventilation and air cleaning. Despite the problems of security the results seem to have been made readily available. Especially interesting in this connexion is some work done in Massachusetts in the so-called "chelating" agents. Ethy-

lene diamene tetra acetic acid ("versene") has been shown to stimulate to a marked degree the excretion of lead in those suffering from lead poisoning, and it is felt that it may also have a practical application to radioactive materials. Some work on this has been done in this country also. Some doubts have been expressed, however, that this particular drug may stimulate the excretion of essential trace elements, a development which might prove difficult to control.

Industrial hygiene is essentially an American approach, and it enjoys the virtues and defects of other American institutions. It shows great energy and drive and the marked characteristics of the vigorous private enterprise that so largely supports it. It lacks, to English eyes at least, coordination. What State control there is, is of 48 different varieties. Americans fight shy of the regular coordinated State inspection of industry so well established in Europe, and in consequence they lack some of the advantages of that system. In particular they lack national accurate statistics of the incidence and morbidity of industrial disease. While one may well be lost in admiration for the forceful and painstaking efforts which industrial hygiene is making to control the industrial environment there is little accurate data by which to judge its success.

While compensation insurance, the backbone of the American system, has done so much to stimulate the control of known occupational hazards, it may not to the same extent encourage either the medical profession or the industrial hygienists to discover new industrial diseases and hazards. British industry as a whole has come to accept perhaps more readily the implications of research into industrial disease and does not now to any marked degree contest their results. American industry in insisting on scientific proof of toxic dangers and their presence in the atmosphere seems to delay to some extent the application of measures of control, and this may account for some occupational diseases being undiagnosed in the United States while in this country they are accepted without controversy.

Industrial Medicine

An older development than hygiene, industrial medicine in the United States, though now largely a growth of the Workmens Compensation Act was originally based upon the first-aid department, or the "plant hospital" in the larger factories. The earliest industrial medical officers were drawn from the ranks of the surgeons, and dealt largely with physical trauma. Industrial medicine has, however, taken on new functions and is now considered for recognition as a specialty.

While the American industrial medical officer of today is very different from his predecessor, he is by no means always an industrial toxicologist, for the problems of industrial toxicology are left largely to the industrial hygienist. Indeed several large plants have medical departments and also industrial hygiene departments, in many cases wholly separate from each other.

Industrial medicine is conceived largely in the United States as clinical medicine applied to the factory as a group rather than to the individual as in private practice. It is preventive in its emphasis on keeping people well rather than in curing disease. The purpose of the medical department is to keep people at work and to keep them efficient while they are at work. This has led to a development which is of considerable importance, namely, the pre-employment medical examination. In some firms there are also periodical examinations which may extend from the office boy to the president of the company. A variety of forces have been responsible for this development, the first and obvious one being to make sure that the company does not employ any person who is physically incapable of doing the work assigned to him. This goes hand in hand with the American emphasis upon fitting the worker to the job and in finding out both his physical and psychological capabilities. This desire not to employ people who are physically unfit for particular work has by pressure of events and particularly by pressure of compensation law widened the scope of these examinations to exclude a variety of people who may well be "bad risks". Since in most States where compensation laws are in force compensation is payable for aggravation of an existing condition, and since aggravation is interpreted both by the compensation tribunals and also by the courts in an ever wider sense, the pre-employment medical examination tends to become ever more strict. A striking recent example has already been mentioned, namely, that since insurance companies are now being forced to pay compensation for loss of hearing in noisy occupations, it has become important to determine the hearing ability before employment.

Periodical medical examinations are also a means of assessing damage to the individual from his occupation, and in this respect are an important check on the work of the industrial hygienist in controlling the hazards of an industry. They may, however, be used as a substitute for controlling the hazards by enabling the industry to remove employees from dangerous environments before they develop symptoms which are compensatable. While this view may not be widespread it certainly exists.

Pre-employment medical examinations in conjunction with aptitude testing have become standard procedure in most large American works, and though they have run into some difficulties with trades unions, the system has so far never been applied extensively except in periods of full employment. The main object of the medical department in its physical examinations, both the pre-employment and also, where practised, the periodical, is to prevent employment of the physically handicapped in occupations which may aggravate their condition. It is, however, no great advance to use this technique to prevent the employment of the physically handicapped at all. In time of serious unemployment the pre-employment physical examination might be used as a weapon to prevent all but the most healthy individuals obtaining work. Already in those factories where periodical medical examinations are undertaken, problems have arisen in connexion with the ageing employee who is declared by the medical

department to be physically unfit for the job that he is now performing and is forced to accept some other job. Even if this does not involve lowering of pay, it may involve loss of seniority which where "first in, last out" rules are applied, is a source of considerable bitterness.

The treatment of injury is, of course, always a problem and most large plants have well set up and lavishly equipped medical departments which sometimes include a small operating theatre. Most space is generally given, however, to examination rooms due perhaps to the higher labour turnover of American industry. While industrial medical officers are now trained in industrial toxicology and may well have considerable knowledge of toxic risks, one does not gain the impression that this side of industrial medicine takes a very prominent place in their outlook or activity.

A remarkable reduction in lost time from accidents has been noticed in factories where a medical department has been set up. The exact relationship between the work of a medical department and these reductions is not known, but it must be connected to some degree with improved treatment of injury so that infection rarely occurs and with getting injured persons back to work more quickly. In this respect a well-run department may induce a man to stay at work though injured, since he can get regular medical attention within the works itself, whereas if he is taken off to an outside doctor or to the casualty department of a hospital he is normally sent home and not back to work. In fact it is a policy of a plant medical department to prevent minor injuries becoming major injuries. The great attention given by American industry to preventing workers staying away from work because of accidents and to get them back when they have stayed away, is of considerable interest, for there can be little doubt that the rehabilitative effects of work, even of the lightest character, are greater than the best influence that can be brought to bear in the home. And in this the medical departments of American industry are doing very important work.

Conclusion

It is foolish for anyone to imagine that he can assess the institutions or the way of life of another country wholly objectively, for however hard we try our reactions are conditioned to some extent by the opinions and, above all, the prejudices which we bring from our own land. This is particularly true of the Americans and the British, for so often our similarities in outlook and in language serve to conceal the very marked differences between the two countries; we are, as Bernard Shaw said, "two nations divided by a common language."

There is, however, one marked impression left in the mind when considering industrial health in the United States. It is the lack of coordination of the efforts of the various persons interested in the subject. To say this is not to be unaware of the national background provided by American history that probably makes this inevitable. America has no industrial enforcement service such as the Factory Department in this country to establish the minimum standards of industrial health without fear or favour and without reference to geographical barriers. More important, as a result, she has no statistics of industrial disease for the nation as a whole. It is this more than anything which makes it difficult to assess the success of American enterprise in this realm.

THE APRIL (1954) ISSUE

The April (1954) issue contains the following papers :—

Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Part I. The Role of Aniline, Benzidine, Alpha-Naphthylamine, and Beta-Naphthylamine. By R. A. M. Case, Marjorie E. Hosker, Drever B. McDonald, and Joan T. Pearson.

Tumours of the Urinary Bladder in Dogs after Ingestion of 4-Aminodiphenyl. By A. L. Walpole, M. H. C. Williams, and D. C. Roberts.

An Industrial Health Service in Norway. By Haakon Natvig.

Fatal Emphysema in Two Men Making a Copper Cadmium Alloy. By Ronald E. Lane and A. C. P. Campbell.

A Study of Boils at Three Collieries. By O. P. Edmonds, R. H. P. Fernandez, and L. B. Bates.

Individual Differences in Accident Susceptibility Among Coal Miners. By J. W. Whitfield.

The Toxicity of Nitrogen Pentoxide. By W. M. Diggle and J. C. Gage.

The Development of Lymph Nodes after Injection of Flint of Variable Size into the Lungs of Rats. By G. Nagelschmidt, E. S. Nelson, E. J. King, and C. V. Harrison.

The Effect of Oiling the Cotton on the Airborne Contamination in Card Rooms. By D. G. Drummond, Mary Hamlin, J. K. Donoghue, and F. Brownsett.

Miscellanea :

A Simple Micromethod for the Determination of Lead in Small Amounts of Blood. By P. E. Cornish and D. O. Shiels.

Three Approaches to the Study of Personality. By Alastair Heron.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

Second Conference of the British Occupational Hygiene Society

R. J. SHERWOOD

The second full-day conference of the British Occupational Hygiene Society held on April 6, 1954, at the London School of Hygiene and Tropical Medicine was opened by the incoming President, Professor E. J. King, who paid a tribute to Dr. Bedford, the retiring President, for his work in founding the Society and ensuring the success of the first year of its life.

He expressed a welcome to all visitors, especially those from overseas.

The subject discussed at the conference was air contamination in industry and its effect on the health of workers. The first paper to be presented, " The Investigation of Atmospheric Contaminants in Factories ", was delivered in two parts.

In introducing the first section on fundamental aspects, Dr. M. W. Goldblatt, Head of the Industrial Hygiene Laboratories, I.C.I. Ltd., stressed that present standards of the medical supervision of workers must be considered minimal. While big organizations had safety and medical departments, this was not true of the 230,000 factories which employed fewer than 100 workers. The only medical contacts that the managements and workers of these factories had were with the appointed factory doctors, who dealt primarily with young persons and particular trades.

It was true that very few cases of poisoning were notified, but the statistics gave a wholly misleading picture of conditions since mild chronic poisoning was probably never reported. Modern medical diagnosis and treatment made it possible for men to stay at work even when absorbing toxic substances. It was probable that chronic poisoning was widely incident in industry.

To ensure that conditions were safe when an atmospheric contaminant might be present, it was essential that, wherever possible, quantitative measurements of the contaminant be made. Merely to show its presence or absence meant nothing. Where toxic materials were present in measurable amounts and were being absorbed by the work people not only had air samples to be taken but also adequate records had to be kept so that over a period of time it might be possible to correlate the clinical histories and environmental concentrations. There was no such thing as an " allowable " concentration ; or rather, the " allowable " concentration always had to be zero. In practice, it was necessary to accept a " design " concentration as a criterion for the engineer to use in the design of equipment. The target always ought to be zero.

Dr. Goldblatt warned his audience against the wrong use of tables of maximum allowable concentrations. In particular, it was misleading to compare materials having different effects. This had been done by listing substances in zones of equi-toxicity ; that was by placing several materials having similar maximum allowable concentrations in each zone. Each zone might then contain materials as different as irritants and narcotics which, on the surface, appeared to be equally toxic. Nevertheless, the narcotic, possibly causing insidious, chronic poisoning might well be the greater menace to health. It was essential to take notice of the nature of the material in assessing the possible risk of exposure. It was also most dangerous to predict the toxicity of a material by chemical analogy with others having a similar structure.

The second section, " Practical Aspects ", was presented by Dr. J. C. Gage, Head of the Biochemical Section, Industrial Hygiene Laboratories, I.C.I. Ltd., who said that it was essential that analytical methods were applied wherever possible and in the correct manner to determine whether work people were absorbing toxic materials.

The main requirements for a method for general application in a factory were that it should be inexpensive, self-contained, and unobtrusive ; it should give an immediate result, should be so simple and reliable that a laboratory assistant or foreman could operate it, and it should be adequately accurate and specific. Such tests were particularly useful for testing air purity in a confined space or tank before workmen went in.

Tests of this type were exemplified by the simple test paper or bubbler methods described in the leaflets, " Methods for the Detection of Toxic Gases in Industry ". Recent years had seen the development of indicator tubes for carbon monoxide and other substances. It was hoped that this principle would have a wide application.

More complicated instrumental methods were available which included the mercury vapour detector using ultraviolet light absorption, and the infra-red analyser which was available for numerous materials. Some of these instruments were capable of giving a continuous written record of atmospheric concentrations over long periods of time, or could be designed to give an automatic warning if safe limits were exceeded. These instruments had a useful, though limited, application to atmospheric studies in factories.

The first afternoon paper, " The Measurement of Dust Exposure for the Control of Pneumoconiosis ", was presented by Dr. B. M. Wright, of the Pneumoconiosis Research Unit, who said that the present lack of agreed safe limits for dust exposure was due partly to lack of agreement on the methods of making the measurements which were required to establish such limits, and partly to the fact that measurements had not been made on a big enough scale.

To set up safe limits, the relationship of a certain level of exposure (affected by the concentration and composition of the respirable fraction of the airborne dust to which workers were exposed and the duration of their exposure), and the incidence and severity of pneumoconiosis amongst those exposed had to be determined. The level of exposure which would be accepted as safe would then depend on what incidence and severity of pneumoconiosis was considered tolerable.

It was essential that in measuring concentrations of dusts producing pneumoconiosis, only respirable dust be

taken into account. Particles or aggregates above 5 or below 1 micron should not be included. The only instrument in common use that enabled this to be done was the thermal precipitator which collected the dust without breaking up the large particles or aggregates. Its chief handicap was that relatively short-term samples were taken and assessment of average conditions over a period of a week or more became laborious.

The essential requirements of a suitable sampling instrument were to enable an estimate to be made of the concentration and composition of airborne dust particles and aggregates in the respirable size range ; to yield a sample which can be reasonably easily and accurately assessed ; to be capable of integrating its exposure over at least one working week ; to be cheap, robust, light, portable, self-contained, and automatic. Until such an instrument had been produced and used over a period of many years, safe limits of dust exposure could not be established with any precision.

Dr. Wright displayed several new pieces of sampling apparatus, including a double aspirator for the thermal precipitator, an automatic sedimentation cell, and a selective mass-sampler.

The final paper of the conference was presented by Dr. W. G. Marley, Head of the Division of Health Physics, Atomic Energy Research Establishment, Harwell, on " Permissible Levels of Exposure to Ionising Radiations and Radioactive Materials ".

With the development of atomic energy and the use of artificial radioactive isotopes it had become necessary to examine early information on permissible levels of exposure to *x* rays and gamma rays, and to extend their application to the new substances.

The work in various countries had been reviewed by the International Commission on Radiological Protection. At the 1953 meeting of the International Congress of Radiology, the Commission recommended values for the maximum permissible body burden of a wide range of isotopes and of the corresponding levels in air and drinking water. These were to be published shortly.

Dr. Marley discussed the methods of arriving at these recommended values. Wide experience with *x* rays and gamma rays had made it possible to define a basic tolerance for external irradiation and this had been set at 0·3 roentgen/week in the tissue (corresponding in certain circumstances to approximately 0·5 roentgen/week measured with back-scatter on the surface of the body). A further basic tolerance figure from human exposure had been derived from the study of the effect of radium ingestion by radium dial painters, namely 0·1 microgram of radium fixed in the skeleton, which was thought to be safe over a working life time.

Different types of radiation or different isotopes could be compared experimentally and theoretically with these basic criteria, and the permissible level of exposure for the particular radiation or material could be calculated by allowing for the relative biological effectiveness of the particular radiation. Parameters that effected this calculation included the fractional uptake from lungs or gut, the metabolism of the element, the organ of concentration, the biological half-life, and the overall relative toxicity. These had been determined from animal studies and from a limited experience of accidental exposure in men.

To achieve agreement between the various laboratories undertaking research in this field, it was found necessary to define a " standard man " for whom the weight and constitution of various organs had been set. The levels recommended by the International Commission were intended for application to individuals who were exposed in their occupation. Should more than a small fraction of the population be exposed, the genetic effects would have to be considered.

Dr. Marley also discussed problems resulting from exposure due to accident or emergency, where a much more intense level had been present for a short period.

The conference was attended by 150 members of the Society and visitors. Copies of the proceedings will be available from the Hon. Secretary, Mr. Peter C. G. Isaac, Public Health Engineering Laboratory, King's College, Newcastle-upon-Tyne.

The next conference of the Society is to be held on November 1, 1954, at the London School of Hygiene and Tropical Medicine. This will be devoted to discussion of the hazards associated with radioactivity and the use of *x* rays in industry.

Correction.—We regret that in the paper " Fatal Emphysema in Two Men Making a Copper Cadmium Alloy " by Ronald E. Lane and A. C. P. Campbell in the April issue an error was printed. On page 121 the cadmium concentrations should be stated in μg. per 100 g. fresh tissue and not mg. per 100 g.

OBITUARY

EDWARD PROVAN CATHCART
C.B.E., M.D., D.Sc., LL.D., F.R.S.

In the minds of the majority of medical men physiology is apt to be regarded as a purely academic laboratory discipline unduly concerned with the activities of amphibia and of lower vertebrates. This is not necessarily so. We have just lost by the death of Emeritus Professor Cathcart a pioneer who showed by his work that physiology has much to contribute to our knowledge of man in his present-day industrial environment.

Cathcart first graduated in medicine in 1900 and was early attracted to the study of bacteriology. However, when working in Germany he came under the influence of Carl Voit then the foremost authority on human metabolism and nutrition. The die was cast. In 1905 Cathcart's own University of Glasgow appointed him to the Grieve Lectureship in Physiological Chemistry where he continued to work on metabolism in human beings. With F. G. Benedict in the United States he produced in 1913 a classical monograph " Muscular Work, a Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine ".

In 1915 London University appointed Cathcart to the Chair of Physiology in the London Hospital. The first world war was not a period wholly of frustration. Cathcart put his special knowledge at the service of the armed forces ; he was engaged on what would now be called " personnel research". His chief interest lay in the physique of the soldier and in the expenditure of energy during the performance of different military tasks. The results of this work are to be found chiefly in the *Journal of the Royal Army Medical Corps.*

In 1919 Cathcart became the first professor of physiological chemistry in the University of Glasgow. In 1928, when Noël Paton retired from the Regius Chair of Physiology in the same university, Cathcart succeeded him. This translation had no influence on Cathcart's interests. He continued to work on nutrition, on metabolism, he studied physique in human beings, and he tackled the problem of muscular efficiency and of fatigue. But now he had perforce to work largely in the industrial field. Between 1924 and 1940 the Medical Research Council published no fewer than five special reports by Cathcart and his co-workers on the diets of families in different parts of this country. The knowledge thus gained was to stand the country in good stead during the second world war.

It was inevitable that Cathcart should become a member of the Industrial Fatigue Research Board, later the Industrial Health Research Board. He was Chairman from 1933 to 1940. In 1927 appeared his " Physique of Women in Industry ", an I.F.R.B. report and, in 1935, the companion " Physique of Man in Industry ". He was responsible for many other publications on the reactions of human beings to their environment.

Cathcart was rather out of sympathy with many of the popular views of his time. And he had little inhibition about expressing his attitudes. To him industry was made for man, not man for industry. Many of the technical changes which tended to reduce human beings to robot-like cogs in the machine were anathemas. Rationalization of industry, so popular between the wars, and nationalization after the second world war, were alike antipathetic to his conception of the needs of human beings. He felt that too little attention was being paid to the physiology, the psychology and, indeed, to the dignity of man. He demanded that human beings should have work in which they could have personal satisfaction and pride. He looked critically at the ingenuity of the technical expert in industry who too often neglected the human factor just as he looked askance at the tendency of chemists to process our human food out of all resemblance to its natural form. For Cathcart was first and foremost a biologist whose special study was man. His early training in medicine, that finest of all disciplines in biology and indeed in humanity, made him appreciate the importance of the human being. Our growing realization of the value of physiological and medical knowledge in our industrial life is in no small measure due to the pioneer work of Cathcart. It is fitting that we should express our gratitude for a life well spent in the service of mankind.

R. C. GARRY.

RAYMOND HUSSEY

Dr. Raymond Hussey died on April 15, 1953, in Chicago at the age of 69. He graduated from the University of Maryland in 1911. For many years he had been active in the field of industrial medicine and at the time of his death he was a member of the staff of the Council on Industrial Health of the American Medical Association.

Dr. Hussey was a most charming man whose manifold activities and responsibilities during his very busy life made him familiar with the widest aspects of clinical medicine. He was especially competent in the field of cardiology and pulmonary diseases. He had been an Associate Professor of Pathology at Yale. He had been a member of the Rockefeller Institute, Vice-Chairman and Acting Chairman of the Division of Medical Sciences of the National Research Council, and Commanding Officer of the Army Industrial Hygiene Laboratory during World War II. He had had a wide experience as an administrator and was for several years in charge of workmen's compensation for occupational diseases in the State of Maryland.

During the many years of my association with Dr. Hussey, our discussions and conversations were always a delight ; he knew so much about so many phases of medicine. As a professional associate and as a friend, Dr. Hussey was the sort of person one does not forget, and I shall always feel grateful for having known him.

A. J. LANZA.

BOOK REVIEWS

Rudolf Virchow : Doctor, Statesman, Anthropologist. By Erwin H. Ackerknecht. (Pp. 304 ; illustrated. $5.00.) The University of Wisconsin Press. 1953.

It is surprising that 50 years should elapse since the death of Virchow, the most distinguished pathologist and one of the most famous men of the nineteenth century, before the publication of the first full-length study of his career. Its author is Chairman of the Department of History of Medicine at the University of Wisconsin, and one of the few professional medical historians in the United States. He is particularly well qualified for the task for he was born and brought up in the same part of Germany as Virchow, has a medical degree from Leipzig, where he studied under Sigerist, and is an anthropologist. He gives a fascinating account of Virchow's life as a brilliant pathologist and founder of the study of cellular pathology ; as an eminent physical anthropologist ; and as an outstanding political figure and opponent of Von Bismarck, who once challenged Virchow to a duel which was fortunately never fought.

Dr. Ackerknecht makes it clear that this book is primarily an analysis of Virchow's work and not a description of his life, but there is enough information about the man himself to explain a little of his extraordinary ability. Of modest origin, Virchow had from the beginning complete self-confidence, tremendous industry, and an abnormally low need for sleep. He had the capacity to do outstanding work in many fields simultaneously, and, although single-minded and ascetic, he was also approachable, hospitable, and sympathetic to patients. He was a popular teacher but a ferocious examiner, and had very personal opinions on the rights of his assistants to marry, teach, or leave him !

Virchow's diversity of interests in medicine are well illustrated by his discoveries of leukaemia, amyloid disease, and embolism ; his study of sewerage systems ; and his suggestion that the construction of school benches should be based on anatomical measurements. His views on medicine were well in advance of his time, and at a period when there was an overwhelming interest in bacteriology he believed that disease might be overcome by social change and that social factors were the most significant in the complex origin of epidemics. His early training as a military surgeon probably had much influence in the emphasis he put on public health and preventive medicine. He believed that medicine should enter political life, and because of his own political influence he was able to accomplish more in the field of public health than the public health experts of his day. The account of discussions on medical reform in Germany in 1848 has many recent parallels, and it is interesting to find that Virchow advocated free medical education, a year of internship, and better instructional methods to replace lecture courses.

There is only passing reference to Virchow's mistaken views on the origin of black pigmentation in the lungs of coal-miners which retarded research into this problem in Germany for nearly 20 years. Virchow gave his authority to the view that the so-called pathological pigmentation was due not to the inhalation of coal dust, but to the extravasation of blood as a result of hyperventilation in bad air, or perhaps to soot from miners' lamps. Later he changed his mind and differentiated pigmentation of the lung due to coal from other causes of pigmentation. A full account of this controversy is given by Rosen in his " History of Miners' Diseases " (New York, 1943).

In spite of the almost unlimited scope given by its subject this book is a very readable and concise account of Virchow's many activities in just over 240 pages, and there is a useful biographical glossary. It is a book likely to have a wide appeal especially to those concerned with preventive medicine in its widest sense, and with the place of medicine in relation to society.

R. I. McCallum

The Eczemas : A Symposium by Ten Authors. Edited by L. J. A. Loewenthal. (Pp. 267 ; 77 figures, 10 coloured plates. 35*s*.) Edinburgh : E. & S. Livingstone. 1954.

The industrial medical officer wants to know what the dermatologist is thinking about dermatitis. How, for example, does he set about distinguishing dermatitis caused by dust, liquids, and vapour from psychosomatic eczema produced by frustration, fear of incapacity, and resentment ? If " dermatitis " is really caused by sensitization to oil, chemicals, dust, etc., then why does it not get better when the relevant contacts are avoided ? What does the dermatologist know about the reaction of the skin under experimental conditions to substances alleged to damage it ? What is the latest news about the physiology of allergy ? The answers to these questions and to many others are to be found in this beautifully produced and thoroughly readable little book.

Haxthausen's chapter on " allergic eczema " (what most of us would call sensitization dermatitis) is a comprehensive and aesthetically satisfying résumé of recent work which includes his own ingenious skin grafting experiments in identical twins. Ray Bettley's chapter on " contact eczema ", the clinical aspect of the same subject, provides valuable practical guidance in the diagnosis of dermatitis. Otherwise the general tendency is reactionary and it may be thought that the

book represents the views of those who ignore the phenomena of their experience in order to construct a world in which the functions of the cell are personified and microbes become the instruments of Providence. A list of " useful prescriptions " supplies the meretricious perfume unhappily *de rigueur* in writings addressed to the general practitioner.

This little book cannot fail to entertain, and it should help to revive interest in an obscure and unrewarding subject. The Editor is to be congratulated not only on his enterprise but on his very real success in integrating the views of so many talented personalities.

J. H. TWISTON DAVIES

Pulmonary Tuberculosis. By R. Y. Keers and B. G. Rigden ; Foreword by F. H. Young. Third edition. (Pp. 324 ; 150 figures. 24*s*.) Edinburgh : E. & S. Livingstone. 1953.

Both the popularity of this little book and recent advances in treatment have necessitated three editions in eight years. It is well produced but the films suffer the inevitable consequences of reduction in size so that minimal lesions are difficult to see.

It is written easily and clearly with sufficient historical review to whet the appetite without overburdening the student. The chapter on after-care is well done and outlines the help available from the various social services. Perhaps the weakest part of the book is in the statistics on tuberculin testing since neither the methods nor the strengths of tuberculin used are quoted. There also appears to be a discrepancy between the two authors concerning race and tuberculosis, and the important findings of the Prophit Survey are not quoted. Despite these imperfections this book will give the student a thorough picture of an individual with this disease and be of interest and importance to practitioners in the management of their early cases and give them valuable guidance on after care.

J. P. W. HUGHES

Coal Tar and Cutaneous Carcinogenesis in Industry. By Frank C. Combes. (Pp. 76 ; 25 illustrations. 20*s*.) Oxford : Blackwell Scientific Publications. 1954.

This short monograph of 60 pages provides a summary of information relative to the problem of skin cancer. Greatest emphasis is placed upon cancer following exposure to various tars, and the medical man will find the section on the production methods and chemical nature of tars of interest. A disproportionate amount of space, however (about one-sixth of the monograph), is devoted to a discussion of the photodynamic action of light and its relationship to industrial skin cancer.

The author summarizes the early changes produced by exposure to tar as tar burns, tar erythemas (" smarts "), allergic eczematous dermatitis (which he rightly considers as rare), folliculitis, cysts, and melanosis. In discussing the late effects he takes the liberty of redefining the " shagreen " skin of Prosser White as an omnibus title for " alteration in the skin of individuals exposed for long periods to tar and pitch ".

The subject of petroleum cancer and dermatitis from oils is dealt with in some four pages of text which contain the astounding statement that " the carcinogenic properties of crude petroleum and the heavy petroleum oils depend upon their ability to cause follicular hyperkeratoses and acneiform lesions in the same fashion as pitch and carbon ".

The final section on the control of tar cancer is excellent, and includes suggestions for the education and protection of the worker, plant protection, and other general measures.

Numerous references are supplied and these include most of the key references for any person who desires to study the subject. There is, however, no attempt to give guidance as to their relative usefulness. No mention is made in the text of several of the authors' names in the bibliography ; for example, the important work of S. A. Henry is not referred to in the text, and, as judged by the bibliography, the author does not appear to be aware of any publications of this worker later than 1937.

C. N. D. CRUICKSHANK

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Life and Other Contingencies. By P. F. Hooker and L. H. Longley-Cook. (Pp. 312. 22*s*. 6*d*.) London : Cambridge University Press. 1953.

Transactions of the Ophthalmological Society of the United Kingdom, Vol. LXXIII, Session 1953. London : J. and A. Churchill. 1953.

Proceedings of First Congress 1953 of the World Confederation for Physical Therapy. (Pp. 91.) London : The Chartered Society of Physiotherapy. 1953.

Lehrbuch der Arbeitshygiene : Vol. I—Allgemeine Physiologie und Hygiene der Arbeit. By Franz Koelsch. (Pp. vii + 426. DM. 49.–.) Stuttgart : Ferdinand Enke Verlag. 1954.

Occupational Health and Safety. By Gerald Machanik. (Pp. 39.) Pretoria, S.A. : Workmen's Compensation Commissioner. 1954.

First Report of the Expert Committee on Poliomyelitis. W.H.O. Technical Report Series No. 81. (Pp. 69. 3*s*. 6*d*.) London : H.M. Stationery Office. 1954.

Pneumoconiosis Abstracts, Vol. II—1939–1950. (Pp. 518. 80*s*.) London : Sir Isaac Pitman. 1954.

Mental Health and Human Relations in Industry. Edited by Thomas M. Ling, with Foreword by The Rt. Hon. Lord Horder. (Pp. xvi + 268 ; 11 figures. 21*s*.) London : H. K. Lewis. 1954.

Einrichtung und Arbeitsweise einer Blutbank. By W. Heim and P. Dahr. (Pp. 328 ; 36 figures. DM. 33.–.) Stuttgart : Georg Thieme Verlag. 1954.

Textbook of Medicine, 11th ed. Edited by Sir John Conybeare and W. H. Mann. (Pp. xvi + 905 ; 40 figures, 31 x-ray plates. 37*s*. 6*d*.) Edinburgh and London : E. and S. Livingstone. 1954.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the abstracting Journal,* Abstracts of World Medicine, *published by the British Medical Association. The abstracts are divided into the following sections : toxicology ; industrial physiology ; industrial lung disease ; industrial skin diseases ; accidents and orthopaedic surgery ; industrial ophthalmology ; environment ; general. Not all sections will necessarily be represented in any one issue)*

INDUSTRIAL TOXICOLOGY

Berylliosis. Summary and survey of All Clinical Types Observed in a Twelve-year Period. DENARDI, J. M., VAN ORDSTRAND, H. S., CURTIS, G. H., and ZIELINSKI, J. (1953). *Arch. industr. Hyg.*, **8**, 1.

During the 12 years 1940–51, the authors have observed and treated 468 patients suffering from various types of beryllium intoxication—dermatitis, tracheobronchitis, and pneumonitis. The cases were observed at three plants in the Lorain area of Ohio engaged in the extraction and processing of beryllium, in which a total of 3,027 persons were employed during the period, the number employed at the end of that time being 369. [From the figures given it is clear that the labour was largely migratory and the labour turnover considerable, which may have been partly due to fluctuation in demand for military purposes.]

Acute dermal and ocular manifestations appeared in 209 persons ; minor and major respiratory-tract involvement occurred in 222 persons ; the chronic form of the disease was represented by 2 dermal and 35 pulmonary cases.

Three broad types of berylliosis of the skin and mucous membranes were observed : (1) acute dermatitis with and without conjunctivitis and mucositis of the nasopharynx ; (2) beryllium ulcer ; and (3) cutaneous granuloma. The dermatitis presented either as a primary contact type (63 cases) involving exposed surfaces or as an allergic eczematous type (146 cases) due to hypersensitization to beryllium salts and involving exposed surfaces, the genito-crural region, and the lower extremities. The manifestations occurred acutely after 7 to 14 days' exposure to soluble beryllium salts, but recovery was complete in all cases in a like period after removal from exposure and treatment with antihistaminics locally and systemically.

Acute tracheobronchitis, which was due mainly to exposure to fumes, mists, and dusts of beryllium fluoride, ammonium beryllium fluoride, and beryllium sulphate, occurred in 129 workmen. Clinical and radiographic recovery was complete in all cases.

Among 93 cases of acute pulmonary berylliosis, death occurred in 10. Where the exposure was massive the disease appeared after 72 hours, but after less intensive exposure the onset was insidious over a period of several weeks. Radiographic changes appeared 1 to 3 weeks after the onset of symptoms and varied with the stage and intensity of the disability. The chronological sequence of these changes was : (1) diffuse bilateral haziness, usually of the lower lung fields ; (2) irregular soft parenchymal infiltration ; and (3) discrete and conglomerate nodules.

Chronic berylliosis was observed in 35 cases. The onset was usually delayed for a period ranging from a few months to several years after initial exposure—in one case for 11 years. It is of considerable interest that 12 of these cases were classified as non-occupational, 8 being attributed to contact with fumes and dust in a zone within ¾ mile (1·2 km.) of the plant and 4 due to handling contaminated working clothes.

The authors have hitherto regarded the following as essential for the diagnosis of chronic berylliosis : (1) a history of exposure to the dusts or fumes of beryllium compounds ; (2) characteristic pulmonary syndrome, with diminution of pumonary function ; (3) radiological evidence of granulomatosis ; and (4) positive histological and chemical findings on lung biopsy. However, a patch test in which the beryllium ion is regarded as the sensitizing allergen in both skin and pulmonary manifestations has recently been shown to be reliable and will in future obviate the necessity of lung biopsy.

In view of the lack of effective or specific therapy, especially for the chronic pulmonary disease, preventive measures are most important and in the plants concerned have already achieved excellent results. *A. Meiklejohn*

Morphological Alterations in the Brain after Intoxication with Parathion (*p*-Nitrophenyldiethylthiophosphate). [In English]. SIEDEK, H., and THALER, H. (1952). *Arch. int. Pharmacodyn.*, **91**, 194.

In the last few years "parathion" has been widely used as an insecticide in agriculture. In acute poisoning with this insecticide central nervous symptoms predominate. The present study, made at the First Medical Clinic, Vienna University, records the effect of acute and chronic poisoning in dogs, 7 of which were given parathion in doses varying from 8 mg. per kg. body weight to a total of 98 mg. per kg.; in the latter case the dog survived for 22 days with the help of atropine, which

eliminated acute toxicity. Animals which died from parathion poisoning showed extensive hyperaemia and haemorrhages in all parts of the brain and spinal cord. Degeneration of ganglionic cells was also present within 30 hours after the first dose of parathion, and after 22 days degeneration of the myelin sheaths was noted. These changes do not appear to be related to the cardiovascular disturbances. *Derek R. Wood*

Disorder of the Nervous System in Workers with Tricresyl Phosphate. BOCK, E., BOCKOVÁ, V., KAMENÍK, M., SAHÁNEK, O., and STANĚK, J. (1952). *Lék. Listy*, **7**, 490.

At the Neurological and Psychological Clinics of the University of Brno, Czechoslovakia, 59 workers engaged in the manufacture of plastic materials and exposed to the toxic action of tricresyl phosphate, either by absorption through the skin or by inhalation of vapour (or both), were examined by the authors. They found that prolonged exposure may result in a variety of symptoms, mainly related to the automatic nervous system, such as hyperhidrosis, dermographism, trophic disorders, and vasomotor disturbances (with hypotension); other neurological symptoms included polyneuritis (in 15 of their cases, or 25%), insomnia, headaches, and neurasthenia, while there were also signs of the involvement of the extrapyramidal system (in workers under the age of 45) and of the pyramidal tracts. It would appear that tricresyl phosphate absorbed through the skin predominantly affects the peripheral nervous system, whereas by inhalation it more frequently causes lesions of the central nervous system. The autonomic nervous system seems to be affected whatever the route of absorption. Symptoms of mental disturbance—emotional instability, and paranoid traits—occurred fairly frequently.

Suggestions are made for reducing the exposure of workers to tricresyl phosphate, and general hygienic measures are recommended. *Catherine Schöpflin*

Coproporphyrinuria. Study of its Usefulness in Evaluating Lead Exposure. PINTO, S. S., EINERT, C., ROBERTS, W. J., WINN, G. S., and NELSON, K. W. (1952). *Arch. industr. Hyg.*, **6**, 496.

One of the "screening" methods hitherto used to discover workers suffering from lead poisoning has been that of direct measurement of the concentration of lead in the urine. To determine significant exposure to lead in 124 employees at a lead smelting plant the authors estimated the urinary excretion of coproporphyrin III by the improved method of Schwartz and others (*J. Lab. clin. Med.*, 1951, **37**, 843), which showed that the mean normal excretion was 160 μg. a day [about 11 μg. per 100 ml. of urine]. Of the 124 subjects, 32 were judged to have significant symptoms, but not one had the classical picture of lead poisoning, then or subsequently. Of these 32, 27 (84%) excreted more than 40 μg. of coproporphyrin per 100 ml. of urine, as compared with 21 (23%) of the 92 who had no symptoms. Estimation of the urinary excretion of lead gave less definite results, but estimation of the concentration of lead in the blood showed that in 26 (81%) of the 32 patients with symptoms and in 30 (33%) of the 92 without symptoms the blood level was over 95 μg. per 100 g. The distribution of cases according to the basophilic aggregation count appeared to be less definite, while the stippled-cell count was of little value. The 4 patients with the most definite symptoms were among the 7 with the highest urinary excretion of coproporphyrin and among the 9 with the highest urinary excretion of lead. In the series as a whole there was little correlation between a raised concentration of lead in the blood and the urinary excretion of coproporphyrin, but there was a correlation between the latter and the urinary excretion of lead. The authors consider that in lead poisoning estimation of the coproporphyrin content of the urine is of more value than other screening methods. No association between blood pressure and years of exposure was observed.

[The symptoms thought to be attributable to lead are neither listed nor discussed. On the validity of these, always a debatable matter, hangs the whole of this comparative study.] *J. N. Agate*

AVIATION MEDICINE

Aero-otitis: Etiologic and Therapeutic Considerations. TROWBRIDGE, B. C. (1953). *Eye, Ear, Nose Thr. Monthly*, **32**, 500.

The physiological and pathological effects of flight on the ear are described, with special reference to the consequences of inadequate ventilation of the middle ear during recompression. Rupture of the tympanic membrane is a rare complication of aero-otitis media. In most cases the signs and symptoms are aural pain, tinnitus, and low-tone deafness, with retraction and congestion of the tympanic membrane and a serosanguinous effusion into the middle-ear cavity. Aspiration of the middle-ear fluid following double puncture of the tympanic membrane with a fine needle is preferred to conservative treatment. It is claimed that recovery is complete in about 4 days and that the early removal of fluid prevents development of adhesions causing permanent impairment of hearing. In the author's view air travel should be discouraged when acute or chronic infection prevents normal functioning of the Eustachian tubes. In cases of recurrent aero-otitis media the possibility of mechanical obstruction should be borne in mind. *J. A. Armstrong*

Altitude Stress in Subjects with Impaired Cardiorespiratory Function. A Comparison of the Responses of Normal Subjects, Patients with Angina Pectoris, and Patients with Anemia to Hypoxia. MARBARGER, J. P., WECHSBERG, P. H., PESTEL, C. V., VAWTER, G. F., and FRANZBLAU, S. A. (1953). *J. Aviat. Med.*, **24**, 263.

The results are reported of an investigation of the circulatory and respiratory responses to hypoxia carried out at the University of Illinois, Chicago, on three groups of subjects: (1) 10 healthy male subjects aged 21 to 27; (2) 8 patients aged 47 to 77 with angina pectoris; and

(3) 14 patients aged 26 to 70 with chronic anaemia. Each subject was studied at ground level and on exposure to simulated altitudes of 10,000 feet (3,050 m.) and 18,000 feet (5,480 m.) in a decompression chamber, comprehensive analyses of cardiac and respiratory function being carried out. The normal response to the anoxia so induced included an increase in pulse rate and stroke volume, an increase in " useful work " of the left ventricle, a fall in peripheral resistance to blood flow, a slight fall in systolic and diastolic blood pressures, and maintenance of a normal venous pressure. The respiratory rate showed a tendency to rise with the more severe stress, and the oxygen and carbon dioxide content and oxygen saturation of arterial blood fell, the haematocrit value rose slightly, and minor changes occurred in the electrocardiogram (ECG) which were rapidly reversed by oxygen administration.

In the subjects with angina the blood pressure and pulse pressure were increased on initial examination, peripheral resistance was slightly raised, and there were signs in the ECG of myocardial ischaemia. The changes on exposure to altitude resembled those observed in normal subjects with the exception of an upward trend in both arterial and venous blood pressure. Angina was experienced by some members of this group after 10 minutes at 18,000 feet, and reversal of the changes in the ECG was slower than normal on oxygen administration. In the anaemic subjects at ground level the pulse rate, stroke volume, mean arterial pressure, and venous pressure were increased, peripheral resistance was slightly raised, and arterial oxygen content reduced. Their response to altitude differed from that of the other groups only in that the venous pressure rose significantly, the left ventricular work rate rose more steeply, and the changes in the ECG were reversed more slowly. The rise in cardiac output in all groups was achieved by elevation of both pulse rate and stroke volume.

It is concluded that the risk entailed in the air transport of anaemic and anginal subjects seems slight in modern aircraft, especially if oxygen equipment is available.

D. I. Fryer

GENERAL

Effect of Prolonged Exposure to Intense Noise on Hearing Acuity. SATALOFF, J. (1953). *Arch. Otolaryng. (Chicago)*, **58**, 62.

The author has made an audiographic study, with regular otological examinations of 154 men, all under 50 and the great majority under 40, who were employed in testing jet-engines and were daily exposed to a continuous noise with an intensity between 90 and 120 decibels for periods up to 5 years. No subjects were included who showed any conduction deafness or who used ear-protectors. The predominant frequencies were below the level of 600 c.p.s.

His conclusions are as follows. (1) Workers in industry who are exposed to continuous, moderately intense, low-frequency noise may sustain measurable degrees of auditory fatigue daily for many years without suffering any significant degree of permanent hearing impairment. (2) None of the subjects in this study showed any change in hearing acuity in the 1,024 and 2,048 frequency range, and none sustained changes greater than 30 decibels at 4,096 and 8,192 c.p.s. (3) None of the changes could definitely be attributed to the noise being investigated. Subjective hearing loss and tinnitus were rare. It is concluded that, from the observations made in this study so far, the human ear would appear to be more resistant to noise than it is usually thought to be. The author's methods and the apparatus used are described in detail.

F. W. Watkyn-Thomas

Mackenzie Industrial Health Lecture

The Mackenzie Industrial Health Lecture is arranged biennially by the British Medical Association to commemorate Mr. James Mackenzie, the founder of the Industrial Health Education Society. The 1954 lecture was arranged in conjunction with the Association of Industrial Medical Officers and given during the provincial meeting of that Association on July 13, by Dr. M. W. Goldblatt. His subject was " Research in Industrial Health in the Chemical Industry ". The lecture will be published in a forthcoming issue of this journal.

Lodging of Recondite Data

Arrangements have been made whereby the Technical Information and Documents Unit (T.I.D.U.) of the Department of Scientific and Industrial Research will, on the Editor's recommendation, accept the custody of research papers, particularly those touching industry, for which, on account of their length, there is insufficient space in this journal. This mainly concerns ancillary material which, being inessential to the general reader, need not occupy space in the journal, or, possibly, a complete paper of highly specialized interest. It is intended that specialist workers interested should have access to deposited material either in the reading room of the T.I.D.U. or by loan from the Unit at Cunard House, 15, Lower Regent Street, London, S.W.1.

Brit. J. industr. Med., 1954, **11**, 235.

CARBON DISULPHIDE POISONING IN VISCOSE RAYON FACTORIES *

BY

ENRICO C. VIGLIANI

From the Institute for Industrial Medicine, University of Milan

(RECEIVED FOR PUBLICATION JUNE 18, 1954)

The manufacture of rayon by the viscose process exposes workers to the hazards of carbon disulphide (CS_2) poisoning. When the viscose industry was started the toxicity of carbon disulphide was scarcely known among manufacturers, and the processes used were primitive ; this resulted in many cases of CS_2 poisoning in all those countries where viscose plants had been established. Since then, technicians, besides trying to increase and improve production, have had to solve the problem of protecting workers against the hazards of CS_2.

Italy was one of the first countries to undertake the production of rayon and staple yarn by the viscose process. Until 1936 Italy was one of the leading European producers of rayon and staple. This industry was afterwards greatly developed in other countries and Italy now ranks third ; the output in 1951, however, was 137,000 tons, that is, one-fifteenth of the world's production (Viviani and Graziano, 1952).

The viscose industry in Italy employs at present over 20,000 workers ; unfortunately, there are still cases of carbon disulphide poisoning, but since the beginning of the industry the clinical features of the intoxication have undergone a marked change.

The greatest expansion in the viscose industry in Italy was from 1924 to 1927, during which period production was trebled, increasing from 8,000 to 26,000 tons. In those years the limited preventive measures and the frequent modifications of processes must have caused many cases of intoxication, but, since CS_2 poisoning was not a compensatable occupational disease until 1934, we have no available data as to its incidence.

In 1933, Ranelletti collected in a monograph 80 published cases of carbon disulphide poisoning which had occurred in Italy. The incidence of symptoms was acute psychosis 52%, anaemia and exhaustion 17%, polyneuritis 17%. In newer statistics by Ranelletti, published in 1935, the percentage of polyneuritis had increased to 25%.

Between 1928 and 1934 Quarelli and his colleagues described some cases of Parkinson's disease and other extrapyramidal syndromes as due to carbon disulphide poisoning.

At the eleventh Italian Congress of Industrial Medicine in 1934 Quarelli stated that he had seen many cases of poisoning in the previous few years. Symptoms of the disease were a decrease of muscular strength, and sexual weakness, hypo-excitability of the nerves and muscles, particularly the peroneus, and, in almost 30% of the cases, signs of extrapyramidal involvement. The existence of an extrapyramidal syndrome in carbon disulphide poisoning was later acknowledged and confirmed by others, not only in Italy. In the United States, Hamilton and Lewy (1939) collected 120 cases of poisoning, 33% of which showed extrapyramidal symptoms ; Gordy and Trumper (1938) described 21 cases of poisoning, five of which involved extrapyramidal symptoms.

Statistics of the Italian Institute for Insurance against Accidents and Occupational Diseases show that from 1934 to 1937 83 cases of carbon disulphide poisoning received compensation ; the majority of them occurred in viscose factories. Owing probably to the large increase in the production of staple yarn, in 1938 alone there were 83 cases, of which one was fatal and 16 involved permanent disability.

I had the opportunity of dealing with all the cases of carbon disulphide poisoning which occurred during 1940 and 1941 in Piedmont, where five viscose plants were operated by a total of 10,000 workers. During that period, because of the war, the production of rayon and staple was pushed to the maximum, and, together with the " black-out ",

* Based on a paper read at the XIth International Congress on Industrial Medicine, Naples, 1954.

diminished ventilation in the rooms, lengthened working hours up to 10 or 12 per day, and improper methods of handling then used for transferring the staple from the washing to the bleaching machines, outbreaks of carbon disulphide poisoning occurred in two of the largest plants*. I myself observed 100 cases. The incidence of CS_2 poisoning and CS_2 concentrations in the most hazardous section of the two plants at the end of 1941 are shown in Table 1.

TABLE 1

DISTRIBUTION OF 100 CASES OF POISONING OBSERVED IN 1940–41 AND CS_2 CONCENTRATION IN TWO PLANTS

Department	No. of Cases	CS_2 Concentration (mg./l.)		
		Average	Maximum	Minimum
Churn	11	0·45	0·87	0·11
Staple spinning	9	0·60	1·00	0·22
Staple bleaching	71	1·00	2·50	0·00
Rayon bobbin washing	5	0·45	0·75	0·15
Others	4	—	—	—

In the staple bleaching rooms workers discharging the washing machines and feeding the bleaching machines, as well as those cleaning the gully gratings, were exposed for four to five hours a day to CS_2 concentrations of 1·0 to 2·0 mg./l. No cases occurred in rooms where the CS_2 concentration was below 0·15 to 0·20 mg./l.

From the study of the relationship between the CS_2 content of the air and the occurrence of poisoning, I was led to the following conclusions (Vigliani, 1946):—(1) Concentrations higher than 0·50 mg./l. with a maximum of 2 mg./l. are liable to poison workers within four to six months, in some cases in only two months. (2) Concentrations of 0·40 to 0·50 mg./l. are apt to cause chronic intoxication after one or more years of work. (3) A few cases of mild poisoning were caused by concentrations of 0·20 to 0·30 mg./l.

The findings of the outbreak in 1940–41 show a high incidence of polyneuritis, usually localized in the lower limbs. Table 2 shows the most commonly occurring symptoms and their incidence.

Polyneuritis was included only when absence or severe weakening of the Achilles and/or patellar reflexes was found: the symptoms were tiredness and heaviness of the legs, difficulty in walking, pains in the knees, paraesthesias and hypo-aesthesias. Paresis never developed into a complete leg paralysis, and even muscular hypotrophy was never very severe. Many cases of polyneuritis did not improve in the course of years. Zeglio (1946) examined 20 of my cases after five years and found one recovered, four improved, five unchanged, and 10 worse.

*Similar outbreaks occurred during World War II in many European countries, e.g., in Finland, France, Belgium, Poland, Holland, Germany (Noro, 1944; Langelez, 1946; Paluch, 1948; Merlevede, 1951; von der Heydt, 1954).

TABLE 2

INCIDENCE OF SYMPTOMS AMONG 100 CASES OF CS_2 POISONING OBSERVED IN 1940–41

Manifestations	%
Polyneuritis	88
Gastric disturbances	28
Headaches	18
Vertigo	18
Sexual weakness	16
Tremors	16
Myopathy	15
Psychoses	5
Extrapyramidal	3
Optic neuritis	2
Hemiparesis	1
Pseudobulbar paralysis	1

Fifteen per cent. of the cases examined showed myopathic symptoms in the calf muscles. Clinically, there was a feeling of heaviness and stiffness of the leg, with hardening and contracture of the calf which made walking very painful. The idiomuscular excitability was increased up to a true myotonic contraction; the muscular chronaxie in these cases was greatly increased, up to a value of 8 to 10 σ. In some patients the myopathic alterations of the calf were really severe. A biopsy was performed on one of the severest cases. Histological examination showed hypertrophy of the muscular fibres, accompanied by atrophy, vacuolar, wax and hyaline degeneration in other fibres, and scars without pericellular fat infiltration. As far as I know, an alteration of this kind had not yet been observed in carbon disulphide poisoning. In two other cases observed in 1953 the clinical diagnosis of myopathy was confirmed by biopsy (Vigliani, 1953).

The first of these two patients (San. E., aged 52) had worked for 26 years in the rayon and staple yarn spinning and washing rooms of Plant P. near Milan. In 1943 he had polyneuritis, but before a complete cure was achieved he returned to his job. In 1953 weakness of the legs with paraesthesia, headaches, gastric disturbances, loss of libido, and painful cramps associated with a feeling of tension and rigidity in the calves. In the morning before getting out of bed he was obliged to massage the calves for some minutes in order to soften them and to avoid cramps. On examination the leg muscles and especially the calves were contracted and very tender and the Achilles reflexes were absent. A biopsy of the calf was performed and showed myopathic alterations (Fig. 1).

In my file of 100 cases seen in 1940–41, five cases were labelled as having CS_2 psychosis, but only one case out of five showed acute psychosis. The others had chronic psychoses associated with extrapyramidal symptoms, or mental deterioration connected

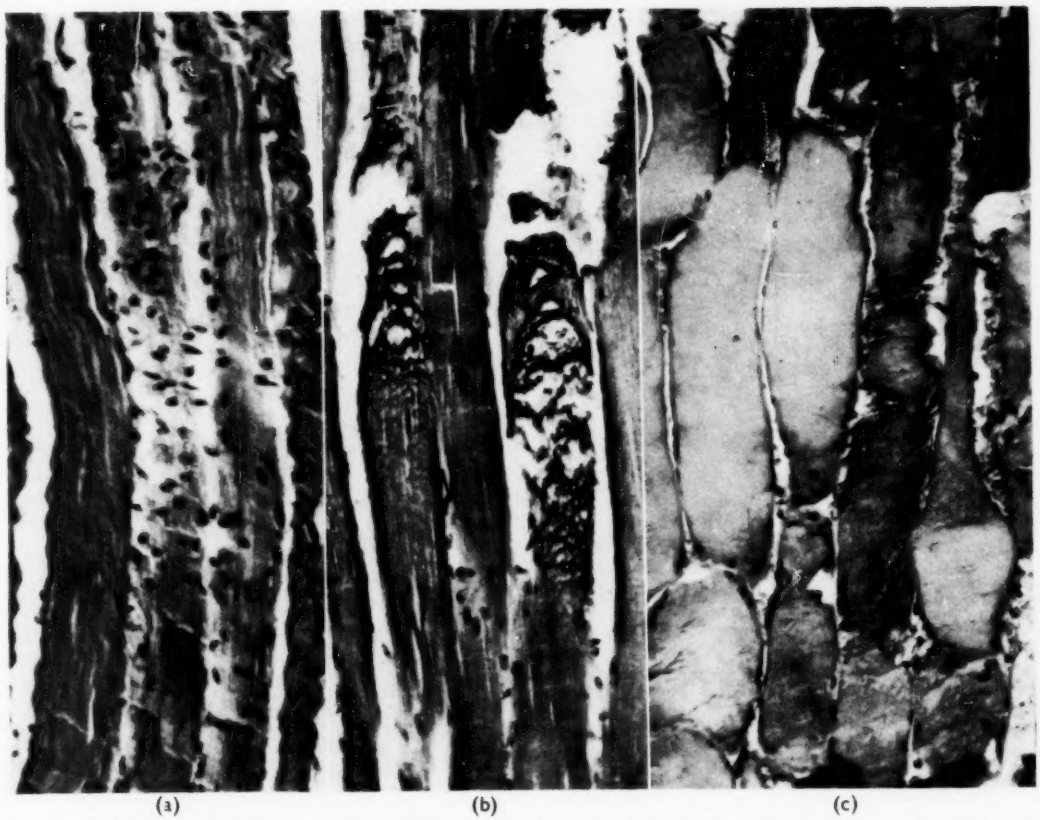

FIG 1.—Photomicrographs from a biopsy of the gastrocnemius in a case of chronic CS_2 poisoning with myopathy seen in 1953 (San. E.).

(a) Sarcolemma nuclei invading a muscular fibre (× 200); (b) Hydropic-vascular degeneration of two muscular fibres (× 200); (c) Swelling and waxy degeneration of muscular fibres (× 200).

with severe polyneuritis or general manifestations. The case with pseudobulbar paralysis and the case of hemiparesis are very similar to those I frequently observed in the later years ; they concerned workers exposed for many years to CS_2 and could be considered as cases of vasuclar encephalopathy.

In 1942 I was transferred from Turin to Milan and I have therefore lost sight of the cases of CS_2 poisoning in the viscose factories of Piedmont but began examining those from the plants of Lombardy. There were five plants near Milan for the production of viscose, with a total of 8,000 workers. Most of the cases observed, however, came from two plants only. At the start, I again saw some cases of polyneuritis similar to those observed in Turin. Later, the symptomatology and the features of the cases changed into a vascular diffused encephalopathy with or without focal lesions.

The first cases were diagnosed as atherosclerotic dementia, or pseudobulbar paralysis, or diffuse encephalomyelitis, or cerebral thrombosis not of occupational origin. The cases gradually became more frequent and showed certain peculiarities, such as occurrence at a relatively youthful age and long-term exposure to dangerous CS_2 concentrations, suggesting a relationship between chronic exposure to CS_2 and the occurrence of the disease. Between the years 1943 and 1949 Dr. Cazzullo and I collected and published 16 of such cases (Vigliani and Cazzullo, 1950).

From 1950 to 1953 I have seen an increasing number of similar cases : five in 1950, seven in 1951, 13 in 1952, and two in the first quarter of 1953, so that the total number of cases observed since 1943 is now 43. Twenty-one came from C. factory, 18 from P. factory, two from a third, and two from a fourth factory ; one patient had worked in three factories.

Table 3 shows the distribution of the cases in the departments of C. and P. factories.

For the 43 workers the average working period by age groups was as in Table 4.

TABLE 3

DISTRIBUTION OF 39 CASES OF CHRONIC CS_2 ENCEPHALOPATHY IN TWO VISCOSE PLANTS DURING 1944–53

Department	C. Factory			P. Factory		
	No. of Workers	No. of Cases	Average Years' Work	No. of Workers	No. of Cases	Average Years' Work
Rayon spinning and vacuum cleaning	225	7	24	229	10	25
Staple spinning and bleaching ..	180	12	18	55	4	20
Churn and viscose press filters ..	170	2	20	135	4	24
Total (average) ..	575	21	(20)	419	18	(24)

TABLE 4

AGE AND YEARS OF WORK OF 43 CASES OF CHRONIC CS_2 ENCEPHALOPATHY

Age	No. of Cases	Average Years of Work
37–39	4	17
40–49	10	19
50–59	21	21
60–68	8	28
Average 52·8	43	21

In the Appendix 43 cases which I have observed up to the first quarter of 1953 are presented. I have also indicated in each case the degree of disability estimated during the course of clinical studies at the Clinica del Lavoro.

The disease has a most characteristic pattern. There is a slow, deceitful beginning, with paraesthesias, asthenia, difficulty in walking, mental deterioration, spastic paresis, alteration of speech, up to a fully developed pattern of pseudobulbar paralysis. The slow course of the disease was often punctuated by episodes of more or less transient hemiplegia. The history of 25 workers over 43 years of age showed that they had had a stroke, and the examination a spastic hemiparesis. Hemiparesis was found even when the patient had never complained of a stroke. Eleven showed signs of extrapyramidal involvement; of these, six had typical Parkinsonism; one had an alternate Millard-Gubler syndrome; one a thalamic syndrome, one a subcortical myokinetic syndrome; two an optic neuritis. The disease has a chronic and progressive course often reaching pseudobulbar paralysis and dementia. Eighteen workers had pseudobulbar paralysis and 15 patients had hypertension. In some cases the blood pressure showed great fluctuations which could easily give way to cerebral accidents; some had signs of nephrosclerosis.

The symptomatology of all cases, the cerebral arteriography, the electroencephalogram, and the fundus oculi of several revealed that this type of encephalopathy was vascular in nature. The necropsy of three patients, one of whom was only 46 years old, revealed a generalized diffuse vascular sclerosis; cerebral atherosclerosis was very marked, the hyaline fibrosis of the media, with a halfmoon-like thickening of the intima, in evidence. The brain and the spinal medulla contained many small foci indicative of softening, with a predilection for the basal ganglia caused by the vascular lesions. In one case the kidney has been examined and glomerulosclerotic, Kimmelstiel-Wilson-type lesions were found similar to those observed by Uehlinger (1952) in four cases of chronic vascular damage of the kidney caused by CS_2.

Although atherosclerosis was manifest in practically all cases, hypertension and vascular spasms should have contributed in some instances to the development of the cerebral lesions. We are now faced with the problem as to whether these atherosclerotic alterations are caused or at least favoured by the chronic action of carbon disulphide. The answer to this question is not an easy one, because we do not know exactly the cause of atherosclerosis. Certainly, any worker can be struck by cerebral atherosclerosis, especially in old age. There are, however, good reasons for the assumption that the cases I have seen were not caused by simple senile or presenile atherosclerosis, but were connected with the exposure to carbon disulphide. The reasons are as follows.

Almost all the cases have occurred in the spinning rooms and particularly in the rayon vacuum cleaning and staple yarn washing rooms, and in the churn rooms of two factories after an average of 20 years' exposure to the hazard. The CS_2 concentration in these departments was, during the period 1938–44, indubitably higher than 0·20 to 0·30 mg./l. Determinations carried out in May, 1943, in the C. plant gave concentrations of from 0·65 to 0·80 mg./l. in the churn rooms, from 0·03 to 0·10 in the rayon spinning room, and from 0·20 to 1·5 mg./l. in the staple spinning and washing room.

Furthermore, we know that cases of chronic poisoning from CS_2, with classical findings of polyneuritis, had been encountered in those departments during the period 1930–43; danger, in the past, had thus been certain and prolonged. From the end of World War II hygienic conditions have greatly improved because of important technical innovations, so that CS_2 concentrations to-day are well under 0·10 mg./l.

From my series I have omitted some cases which only presented a hemiplegia and those in patients over 70 years of age. Even with this limitation,

however, from 1943 up to April, 1953, I have collected 43 cases, 39 of which came from two factories only. In these two factories the churn, spinning, and washing rooms do not employ more than 1,000 workers and out of these only a small portion had been working at the operations for over 10 years. For this reason the percentage of workers struck by diffuse vascular encephalopathy appears to be very high. The true value may be even higher, because it must be considered that I had most probably seen only some of the cases, *i.e.*, those sent to me because of suspected CS_2 poisoning.

Cerebral atherosclerosis usually causes clinical manifestations in those over 60 years of age. The average age of my cases was, on the contrary, 53 ; 15 of these were not yet 50. Among the 35 cases under the age of 60, 16 had no hypertension, which is commonly associated with presenile cerebral atherosclerosis. It is, therefore, reasonable to assume the intervention of a toxic factor as well as that of age.

Some pathological and clinical aspects of the cerebral lesions, and particularly the diffusion of the lesions throughout the brain and the marked changes in the nerve cells, support the assumption of a toxic and not a purely atherosclerotic factor.

In some cases the pre-existence or the coexistence of manifestations of typical carbon disulphide poisoning, such as polyneuritis, was established.

Other observations of cases similar to mine, *e.g.*, one case described by Laudenheimer (1899) in a woman aged 32, the only woman who resisted 10 years' working with CS_2 ; two cases observed by myself in 1940 (Vigliani, 1946), one diagnosed as "pseudobulbar paralysis due to CS_2", and one of hemiplegia ; one case of carbon disulphide vascular disease described by Gsell (1948) ; five cases of "chronic poisoning from CS_2 with a pattern of severe vascular disease" observed by Attinger in 1948 ; and two others, altogether similar to my cases, reported by Attinger in 1952 ; three cases of diffuse cerebral atherosclerosis seen by Dr. Monarca in Piedmont in the last two years ; and some described by Nunziante-Cesàro and Luccarelli (1954), reinforced my assumption.

In dogs with chronic CS_2 poisoning, Lewey, Alpers, Bellet, Creskoff, Drabkin, Ehrich, Frank, Jonas, McDonald, Montgomery and Reinhold (1941) found severe vascular alterations :

> "The marked arteriofibrosis of the cortical blood vessels found in almost all dogs exceeded by far what is usually seen, even in old dogs. Ophthalmoscopic examinations revealed marked angiospasms in the retinal arteries. In other words, chronic exposure to CS_2 creates in dogs a tendency to spastic and fibrotic alterations in the small arteries of the brain and retina. This observation strengthens the probability that high blood pressure in young viscose rayon workers may not be purely coincidental."

FIG. 2.—Ber. L. (Case 5) aged 42. Pseudobulbar paralysis from CS_2. Small arteries of the brain with thickened wall and loss of muscular fibres. Haematoxylin and eosin. × 410.

In cats poisoned for a period of one to three months with 8 to 10 mg./l. of CS_2 for one to three hours a day, Ferraro, Jervis, and Flicker (1941) found gross alterations of the cortex cerebri vessels, with thrombosis and foci of cerebral weakening ; Carratala and Lambre (1951) found also cases of proliferative endovasculitis in various organs of animals poisoned with CS_2.

I have exposed for several months albino rats to concentrations of CS_2 ranging from 0·4 to 0·6 mg./l. for six hours daily. While the controls did not show vascular lesions, the rats exposed to CS_2 gave evidence of initial vascular sclerosis : one rat, which survived for 420 days, showed diffuse and advanced atherosclerosis, similar to that observed in the three human cases cited above. Further experiments are now under way for the

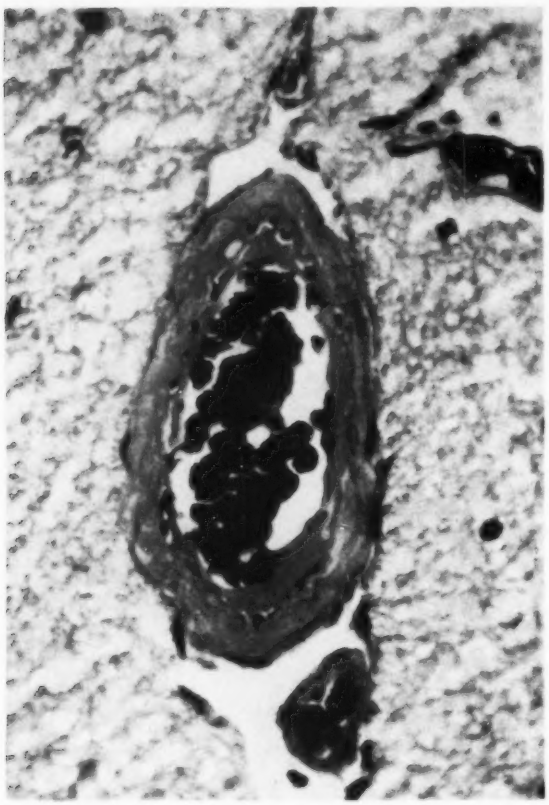

FIG. 3.—Brain of a rat exposed to 0·4–0·6 mg./l. for 420 days showing sclerosis of a small artery, with loss of muscle fibres. Haematoxylin and eosin. × 590.

study of atherosclerosis in rats and guinea-pigs exposed to different concentrations of CS_2.

Nunziante-Cèsaro, Sipala, and Zunini (1952) have recently confirmed on viscose workers some of the experimental results of Lewey; they frequently saw angiospasms in the retinal arteries accompanied by increased vascular fragility and spasms of the arterial side of the capillaries visible to capillaroscopy.

All these facts support the assumption that a very long exposure to hazardous concentrations of CS_2 may cause or greatly enhance a diffuse atherosclerosis of the arterial blood vessels and capillaries, resulting in encephalopathic and/or nephrosclerotic damage. According to this belief, one, and most probably the greatest, section of modern chronic CS_2 pathology should be referred to a toxic vasculopathy,

According to the modern views on the pathogenesis of the atherosclerosis, CS_2 could interfere with the metabolism of lipoproteins. The determination of the β/α lipoprotein ratio carried out in several of our patients gave values as high as 15, whereas the normal is less than 4. Relatively high ratios have been found also amongst workers exposed for several years to CS_2 but without any symptoms: it is possible to conceive that the action of CS_2 consists in the inhibition of the clearing factor in the blood, thus preventing the transformation of the more coarsely dispersed β-lipoproteins in the finely dispersed α-lipoproteins.

The discovery of the existence of a chronic vascular encephalopathy from CS_2 shows that we must review our opinion on the maximum allowable concentration of CS_2 in the air. We had taken as safe concentrations 0·07 mg./l. of CS_2, but are we sure that such a value cannot cause a chronic encephalopathy in 20 to 30 years? The cases I had observed came from plants where concentrations, at least during the war, were very high, and where cases of classical poisoning with polyneuritis were found; but the four cases observed by Uehlinger (1952) had been exposed for 13 to 25 years to concentrations of CS_2 ranging from 0·05 to 0·1 mg./l., with occasional exposures as high as 0·15 mg./l. The possibility of brain lesions having a chronic course and a delayed appearance as those described in this paper should be a sufficient inducement to improve the control and to fix a very low value for the maximum allowable concentration of CS_2.

Summary

The production of artificial textile fibres by the viscose process exposes workers to the hazard of carbon disulphide (CS_2) poisoning. During the Second World War many cases of chronic CS_2 poisoning occurred in the viscose rayon plants of many European countries including Italy. From 1940 to 1941, 100 cases of CS_2 poisoning have been observed amongst workers exposed to concentrations ranging from 0·2 to 1·5 mg./l. in the factories in Piedmont. The most common manifestation observed was polyneuritis (88% of the cases), followed by gastric disturbances (28%), headache and vertigo (18%), sexual weakness and tremors (16%); in 15% myopathic changes of the calf muscles were noted; in 6% of the cases mental deterioration, and in 3% extrapyramidal symptoms were observed.

After the war, working conditions in rayon viscose plants improved considerably so that today it is quite rare to see new cases of carbon disulphide poisoning with classical symptomatology. On the other hand, many cases of chronic vascular encephalopathy developed in workers exposed for 10 to 30 years to atmospheres containing CS_2 vapour in

concentrations which during the war years had been beyond that allowable. Forty-three of such cases seen during the period 1946–53 in four plants in Lombardy are briefly described.

Patients with chronic encephalopathy exhibited symptoms of pseudobulbar paralysis with mental deterioration, frequent extrapyramidal involvement, and focal signs of cerebral thrombosis. Sixteen cases were associated with hypertension and five had kidney insufficiency with albuminuria. Clinical features, electroencephalograms, and cerebral arteriography of several cases and necropsy of three cases revealed that the encephalopathy was vascular in nature and due to a sclerosis of the small arteries and capillaries of the brain and spinal medulla. In one case, a renal glomerulosclerosis of the Kimmelstiel-Wilson type was observed.

Experimental exposure of rats and guinea-pigs for several months to concentrations of CS_2 ranging from 0·4 to 0·6 mg./l. produced hyperplasia and sclerosis in the media and intima of the brain arterioles. The hypothesis is advanced that prolonged exposure to CS_2 can lead to a favourable situation for producing atherosclerosis.

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APPENDIX

Case Histories

Case 1.—Por. C., aged 56, was employed at Plant C. as a spinner for 19 years. He was admitted to hospital in 1943 with scattered neuraxitis with pareto-spastic gait, ataxia, left palpebral ptosis, decrease of strength, very weak Achilles reflexes. Blood pressure was 175/90 mm. Hg. Disability was 80%.

Case 2.—Val. B., aged 37, was employed at Plant C. as a spinner for 15 years. He experienced progressive weakness of the legs, diminished vision, difficulty, and then inability to walk, with paraparesis, ataxia, sphincter disorders, and optic subathropia. He was admitted to hospital in 1945 with acute neuraxitic poussée which rapidly worsened and he died.

Case 3.—Soc. G., aged 56, had been a spinning machine cleaner for 20 years. In 1942 came the onset of manifestations with ataxia, headaches, vertigo, apathy, staggering gait, mental deterioration, and loss of memory. He left work in 1942 and was admitted to hospital in 1945 with a pseudobulbar syndrome and in an advanced state of atherosclerotic dementia. Blood pressure was 160/60 mm. Hg. The patient died while in the hospital. Necropsy revealed severe cerebral atherosclerosis with lacunar state.

Case 4.—Bas. C., aged 44, had been employed at Plant C. as a staple yarn bleacher for 10 years. In 1945 he had neuraxitis from CS_2 with psychosis and reasonless crises of laughter and weeping. He left work in 1945, and was admitted to hospital in 1946 with a pseudobulbar syndrome with a right hemiplegia. Blood pressure was 150/95 mm. Hg. He died in the hospital. Necropsy showed diffuse lipoidosic lesions of the arteries and of the cerebral and meningeal veins with two thrombotic foci, one in the right internal capsule and the other in the spinal marrow.

Case 5.—Ber. L., aged 42, was a spinner for 16 years. He left work in 1940 and was admitted to hospital for the first time in 1940 with a diagnosis of initial

nephrosclerosis and chronic CS_2 poisoning ; in the same year he developed a right hemiplegia. He was readmitted to hospital in 1945 with a typical pseudobulbar syndrome and relative renal insufficiency. Blood pressure was 140/80 mm. Hg. Disability was 100%.

Case 6.—Mel. L., aged 37, had been employed at Plant C. as a spinner for 19 years. In 1941 he had polyneuritis from CS_2 poisoning ; in 1946 weakness and tinglings in the legs. In December, 1946, he had paralysis of the left arm for which he stopped work. He was admitted to hospital in 1947 with a right hemiplegia with hypertension (blood pressure 180/110 mm. Hg). While still in the hospital, the patient suffered from an acute glomerulonephritic episode.

Case 7.—Cam. G., aged 47, had been a churner at Plant C. for 20 years. From 1937 he had paraesthesia of the legs and progressive asthenia ; in the latter years decrease of libido. For these disorders he was transferred to the winding department in 1944. In 1946 he had mental deterioration, loss of memory, and difficulty in walking. He was removed from work in December, 1946, and admitted to hospital in 1947 with diffuse cortical encephalopathy of the pseudobulbar paralysis type with severe psychosis and pareto-spastic gait, and nephrosclerosis with renal insufficiency and hypertension (blood pressure 210/130 mm. Hg). Disability was 100%.

Case 8.—Oli. G., aged 44, had been employed at Plant C. as a spinner for 14 years. In 1938 he had slight CS_2 poisoning, and in 1948 right hemiplegia when he was admitted to hospital. He had slight spastic hemiparesis of the right side with moderate signs of cerebral atherosclerosis, and a blood pressure of 120/70 mm. Hg. Disability was 21%.

Case 9.—Per. F., aged 65, had been a spinner for 25 years in Plant P. From 1946 he suffered from asthenia, difficulty in walking, and giddiness. He left work in 1948, and was admitted to hospital in that year with typical pseudobulbar paralysis with signs of atherosclerotic contracted kidney. Blood pressure was 190/125 mm. Hg. Disability was 100%.

Case 10.—Bog. A., aged 45, had been employed at Plant P. as a spinner for 19 years. In 1945 he had a sudden paralysis of the right limbs with difficulty in talking. He was removed from work in 1946, and admitted to hospital in 1948 with classical pseudobulbar paralysis, crises of weeping, and severe mental deterioration. Blood pressure was 190/125 mm. Hg. Disability was 100%.

Case 11.—Con. A., aged 51, had been employed at Plant C. as a spinner for 29 years. In September, 1949, he had paresis of the right side for which he left his work. He was admitted to hospital in 1949 with encephalopathy with right motor and coordinatory paresis, and signs of pyramidal and extrapyramidal involvement. Blood pressure was 160/110 mm. Hg. Disability was 100%.

Case 12.—Mog. O., aged 48, had been a churner for three years and a rayon bobbin washer for 11 years at Plant P. In 1948 he had CS_2 poisoning and left work in October, 1949. He was admitted to hospital in 1949 with a mild right paresis, tremors, psychic depression, initial renal insufficiency, and mild diabetes mellitus. Blood pressure was 170/95 mm. Hg. Disability was 40%.

Case 13.—Mar. I., aged 52, had worked at Plant P. for 24 years at the preparation of the viscose. In June, 1948, he had a motor deficit of the hands for which he was removed from work and admitted to the Neurological Hospital at Pavia. In 1949 he was admitted to this Institute with a pseudobulbar syndrome with a mild state of dementia, dysarthria, left facial paresis. Blood pressure was 175/90 mm. Hg. Disability was 100%.

Case 14.—Mal. L., aged 57, had worked at Plant P. as a spinner for 28 years, and as a rayon bobbin washer for two years. In 1946 heaviness of the legs, with progressive functional loss led to severe difficulty in walking. He left work in 1948 and was admitted to hospital in 1949 with a pseudobulbar syndrome with dysarthria, mental deterioration, extrapyramidal hypertonia, and spastic paraparesis. Blood pressure was 150/100 mm. Hg. Disability was 100%.

Case 15.—Mor. E., aged 54, had been employed at Plant P. as a spinner for 12 years and as a rayon bobbin washer for five years. In December, 1948, he had a stroke with right hemiplegia for which he left his work. He was admitted to hospital in 1949 with multiple encephalopathic lesions with right hemiplegia, dysarthria, pyramidal and extrapyramidal hypertonia, blood pressure varying from 185/130 to 150/90 mm. Hg. Disability was 100%.

Case 16.—Cav. P., aged 58, had been a rayon bobbin washer for 14 years at Plant C. In April, 1949, he had a slight transitory right-sided stroke. He left work in 1949, and was admitted to hospital in 1950 with a mild right spastic paresis. Blood pressure was 190/110 mm.Hg. Disability was 25%.

Case 17.—Cor. L., aged 68, had worked at Plant P. as a spinner for 28 years, and as a rayon bobbin washer for 10 years. In 1947 he had signs of polyneuritis with difficulty in walking for which he left work. He went downhill and was admitted to hospital in 1950 with severe subcortical diffuse neuraxitis of the pseudobulbar paralysis type. Blood pressure was 170/110 mm. Hg. Disability was 100%.

Case 18.—Lod. G., aged 60, had been a churner at Plant C. for 20 years. In 1947 he had polyneuritis of the legs and left work in 1950. He was admitted to hospital in that year with diffuse encephalopathy with corpus-striatum localization (subcortical myokinetic syndrome) with abulia, mental deterioration, amimia, tremors, hyperreflectivity. Blood pressure was 185/100 mm. Hg. Disability was 100%.

Case 19.—Par. L., aged 60 had worked at Plant P. as a spinner for 23 years. In 1948 he had a stroke with right paresis for which he left work. In 1949 he had another stroke and aggravation of the paresis. He was admitted to hospital in 1950 with mild right hemiparesis with signs of slight extrapyramidal involvement. Blood pressure was 200/120 mm. Hg. He had a moderate loss of the ability to concentrate urine. Disability was 40%.

Case 20.—Ace. E., aged 64, had been employed at Plant P. as a spinner for 30 years. In January, 1950, he had a sudden mild right paresis for which he was removed from work and admitted to the Neurological Hospital of Pavia with a diagnosis of hemiplegic-like pseudobulbar paralysis. At this Institute in 1950 mild pseudobulbar paralysis with moderate loss of power due to a right hemisyndrome was found, blood pressure varying from 140/90 to 110/70 mm. Hg. Disability was 21%.

Case 21.—Fer. C., aged 39, had been a churner for seven years, a spinner and bleacher for eight years at Plant P. From 1941 he had heaviness of the legs and paraesthesias. In 1950 he had tremor and pains in the legs, pareto-spastic gait, and mental deterioration for which he left work. He was admitted to hospital in 1951 with a disseminated sclerosis type of neuraxitis. Blood pressure was 130/90 mm. Hg. Disability was 80%.

Case 22.—Cas. A., aged 47, had worked at Plant P. as a spinner for eight years, and as a rayon bobbin washer for 20 years. In 1949 he had polyneuritis of the lower limbs, and in 1951 right hemiparesis for which he left work. He was admitted to hospital in 1951 with subcortical encephalopathy with left hemiparesis, moderate loss of the ability to concentrate urine, and an encephalogram positive for diffuse cerebral angiopathy. Blood pressure was 130/80 mm. Hg. Disability was 80%.

Case 23.—Mor. G., aged 63, had been a spinner at Plant C for 30 years. In 1949 he had signs of polyneuritis (pains, paraesthesias, staggering gait). He was removed from work in October, 1950, and admitted to hospital in 1951 with diffuse encephalopathy with spastic paraparesis, amimia, mental dullness, tremors. Blood pressure was 160/100 mm. Hg, with oscillations to 220/110. Disability was 80%.

Case 24.—Zam. L., aged 57, had been a rayon bobbin washer for 24 years at Plant P. In April, 1951, he had sudden mental confusion followed by right paresis. He stopped work in April, 1951, and was admitted to hospital in 1951 with diffuse vascular encephalopathy in evolution, with right motor hemisyndrome, optic subatrophy, mild polyneuritis of the legs. An electroencephalogram was indicative of diffuse vascular lesions. Disability was 100%.

Case 25.—Res. A., aged 58, had worked at Plant M. as a spinner for seven years, and as a churn cleaner for three years. In 1949 he had mild polyneuritis from CS_2, left work in October, 1950, and was admitted to hospital in 1951 with polyneuritis of the legs, amimia, and moderate psychic loss. Blood pressure was 140/100 mm. Hg. Disability was 21%.

Case 26.—Vag. C., aged 52, had worked at Plant C. as a churner for 10 years and as a viscose filter cleaner for 10 years. In 1949 he had polyneuritis from CS_2. He was removed from work in 1950 and admitted to hospital in 1951 with diffuse encephalopathy with mild right hemiparesis and signs of polyneuritis in the legs. Blood pressure was 160/100 mm. Hg. Disability was 80%.

Case 27.—Qua. L., aged 59, had been a spinner for 27 years at Plant C. In 1949 he had a right transient hemiparesis then again deficit of the right side, pains, asthenia. He left work in December, 1950, and was admitted to hospital in 1951 with moderate loss of power of the right side. Blood pressure was 125/90 mm. Hg. Disability was 21%.

Case 28.—Gro. L., aged 55, had worked at Plant C. as a spinner for two years and as a rayon bobbin washer for 13 years. From 1947 he had heaviness of the legs with progressive difficulty in walking. He left work in May, 1951, and was admitted to hospital in 1952 with diffuse encephalopathy with symptoms of loss of power, mainly of the right side, mental deterioration, and dysarthria. Blood pressure was 160/90 mm. Hg. Disability was 60%.

Case 29.—Gab. M., aged 56, had worked at Plant P. at the viscose filtering operations for 26 years. In 1932 he had CS_2 polyneuritis of the legs and in 1950 subacute CS_2 poisoning. He left work in November, 1952, and was admitted to hospital in 1952 with diffuse encephalopathy of the pseudobulbar paralysis type with spastic paraparesis, crises of weeping, loss of memory, and giddiness. Blood pressure was 140/80 mm. Hg. Disability was 80%.

Case 30.—Cis. M., aged 39, had worked at Plant M. as a bobbin washer for five years and as a churn cleaner for 11 years. In 1939 he had chronic CS_2 poisoning with polyneuritis. He stopped work in 1952, and was admitted to hospital in 1952 with pseudobulbar paralysis-like encephalopathy with a right hemiparesis, tremors, and psychic deterioration. Blood pressure was 120/75 mm. Hg. Disability was 80%.

Case 31.—Maz. E., aged 44, had been a bleacher at Plant C. for 23 years. In June, 1952, he had a sudden right hemiparesis for which he was removed from work. He was admitted to hospital in 1952 with a right hemiparesis. An electroencephalogram was indicative of diffuse vascular lesions. Blood pressure was 150/110 mm. Hg. Disability was 25%.

Case 32.—Tag. A., aged 61, had been a spinner at Plant C. for 23 years. In 1942 he had slight CS_2 poisoning, and left work in 1942. He was again at work in 1947 in the staple spinning department from which he was finally removed in January, 1950. His first admission

to hospital was in 1950 with diffuse encephalopathy with protuberantial focalization at the right side (paralysis VII, paresis V and VIII). He was readmitted to hospital in January, 1952, for right hemiplegia. Blood pressure was 175/110 mm. Hg. He died at the hospital. Necropsy revealed atherosclerotic-vascular encephalopathy with multiple foci of encephalomalacia.

Case 33.—San F., aged 53, had been employed at Plant P. as a spinner for 24 years. In 1942 he had acute CS_2 poisoning and in 1948 signs of slight polyneuritis of the legs. He was removed from work in May, 1952, and admitted to hospital in 1952 with spastic right paraparesis, tremors, and staggering gait. While in the hospital he had a sudden attack of right hemiplegia. Blood pressure varied from 160/100 to 135/80 mm. Hg. Disability was 100%.

Case 34.—Poz. R., aged 47, had been a spinner for 18 years at Plant C. In 1942 he had slight polyneuritis from CS_2, and in 1951 a sudden right hemiplegia for which he left work. The hemiplegia partially regressed. He was admitted to hospital in 1952 with mild left hemiparesis and signs of polyneuritis (absence of Achilles reflexes). Blood pressure was 150/100 mm. Hg. Disability was 30%.

Case 35.—Pra. E., aged 51, had been a rayon bobbin washer at Plant C. for 29 years. From 1950 he suffered from giddiness, difficulty in walking, and severe psychic deterioration. In June, 1952, he had a right hemiparesis for which he was removed from work and admitted to hospital in the same year with diffuse vascular encephalopathy with severe mental deterioration and motor loss, mainly of the right side. Blood pressure was 180/110 mm. Hg. Disability was 100%.

Case 36.—Par. M., aged 54, had worked at Plant C. as a spinner for 27 years. In 1949 he had paraesthesias, cramps, and pains in the legs, and left work at the beginning of 1950. He first admission to hospital was in 1950 with a luetic Parkinson syndrome; blood pressure was 165/90 mm. Hg. He was readmitted in 1952 with a Parkinson syndrome, dementia, and a thalamic syndrome with violent pains. Blood pressure was 125/85 mm. Hg. Disability was 100%.

Case 37.—Car. A., aged 58, had worked at Plant P. as a churner for 28 years. In 1950 he had signs of polyneuritis and paresis of the left limbs but rapidly improved. In 1951 he had another episode of right paresis for which he left work and was admitted to the Neurological Hospital at Pavia. He was admitted to this Institute in 1952 with a pseudobulbar syndrome. Blood pressure was 200/100 mm. Hg. Disability was 40%.

Case 38.—Car. G., aged 51, had been a spinner for 10 years, a bleacher for four years, and then again spinner for another 13 years. From 1947 he had had paraesthesias and weakness of the legs. In October, 1951, he had a left hemiplegia for which he stopped work. He was admitted to hospital in 1952 with diffuse vascular encephalopathy with left hemiparesis, tremors, hypertonia of the legs, and staggering gait. Endocraniotic alterations were visible radiologically. Blood pressure was 125/85 mm. Hg. Disability was 100%.

Case 39.—Car. C., aged 64, had worked at Plant C. as a painter in the rayon spinning department for 17 years. In 1945 he had a slight episode of acute CS_2 poisoning, and from 1951 progressive weakness of the legs. He was removed from work in July, 1952, and was admitted to hospital in 1952 with initial pseudobulbar syndrome with left hemiparesis, renal atherosclerosis, and obliterating endo-arteritis of the right leg. Blood pressure was 210/130 mm. Hg. Disability was 100%.

Case 40.—Cap. D., aged 57, worked for 12 years at the feeding and discharging of the staple bleaching machines. In July, 1951, he had a left hemiparesis for which he left work. He was admitted to hospital in 1952 with alternately the Millard-Gubler syndrome and dementia. Blood pressure was 150/90 mm. Hg. Disability was 100%.

Case 41.—Ado. L., aged 47, had been a spinner at Plant C. for 23 years. In 1949 he was first admitted to the hospital with polyneuritis of the legs and central lesions causing considerable intellectual and emotional deterioration. He left work in 1949, and was readmitted to hospital in 1952. The signs of polyneuritis had disappeared, but he showed remarkable manifestations of psychic deterioration with hysteria-like gestures. Blood pressure was 120/80 mm. Hg. Disability was 50%.

Case 42.—Mon. V., aged 58, had worked at Plant C. as a bleacher for six years, and as a rayon bobbin washer for two years. In 1947 a left hemiparesis partly regressed, but severe static and intentional tremor of the limbs remained. He left work at the end of 1951, and was admitted to hospital in 1953 with a right hemiparesis on an atherosclerotic base in a psychoneurotic subject. Blood pressure was 200/120 mm. Hg. Disability was 50%.

Case 43.—Vil. G., aged 55, had been a rayon bobbin washer for five years at Plant C. After two years of work he had slight hypertension and a Parkinson hemisyndrome of the right side. He left work in October, 1952, and was admitted to hospital in January, 1953. Parkinsonism was more marked on the right side with central paresis of the right facial nerve. Blood pressure was 185/110 mm. Hg. Disability was 70%.

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INFECTIVE PNEUMOCONIOSIS

I. THE INFLUENCE OF DEAD TUBERCLE BACILLI (B.C.G.) ON THE DUST LESIONS PRODUCED BY ANTHRACITE, COAL-MINE DUST, AND KAOLIN IN THE LUNGS OF RATS AND GUINEA-PIGS

BY

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The close association between silicosis and tubercular infection has long been recognized. In South Africa, Mavrogordato (1926) and Strachan and Simson (1930) concluded that infection played an important part in the development of the disease. Policard (1933) was of the opinion that practically all cases of silicosis were complicated by tuberculosis. Kettle and Archer (1933) observed that infective silicosis was more common in Great Britain than simple silicosis. By infective silicosis was meant " the modification in a dusty lung of the reaction of a chronic low-grade infection, frequently tuberculosis, in the direction of increased fibrosis ", a definition first used by Simson, Strachan, and Irvine (1931). Gye and Kettle (1922) showed that tubercle bacilli proliferated readily in necrotic lesions produced in mice by the inoculation of silica into the interstitial tissues. Kettle (1927) proved that the proliferation of the bacilli was not dependent on the presence of necrotic tissue, but on the actual presence of silica in the lesion. Other workers found that in experimental animals attenuated or dead tubercle bacilli produced proliferating lesions in the presence of silica (Gardner, 1929 ; Cummins, 1940 ; Vorwald and Delahant, 1938 ; Vorwald, Dworski, Pratt, and Delahant, 1950). Gardner (1930) showed that healed tubercular foci which had been produced originally by a low virulence strain were reactivated as a result of exposing the animals to silica dust inhalation. This capacity for new growth on the part of the organisms was not due to an increase in their virulence, since subinoculation from these animals did not produce anything other than the lesions characteristic of the strain. Policard (1939) and Sen (1939) also demonstrated the reactivation of latent tuberculous infections in animals in the presence of silica. Kettle (1932) found that living tubercle bacilli, introduced into the general circulation of mice, proliferated in interstitial lesions previously produced by inoculation with silica, siliceous dust, shale and kaolin, while no growth of bacilli was seen in lesions produced by inert substances such as iron, carbon, and aluminium. By a combination of dust and infection Kettle (1934) produced a degree of fibrosis which could not be obtained from the action of either factor alone. He introduced into the lungs of guinea-pigs a suspension of killed tubercle bacilli from an avirulent strain (B.C.G.) with and without kaolin dust. The usual active infection which results from the presence of live organisms was thus replaced by a transient one which, while merely accelerating the pneumoconiotic process, would not dominate the histological picture.

Several workers have reported a high incidence of tuberculosis among coal-miners whose lungs show the condition known as progressive massive fibrosis (Cummins, 1931 ; Belt and Ferris, 1942 ; Rogers, 1946 ; Gough, 1947 ; Fletcher, 1948). Tubercle bacilli have been demonstrated in the lesions in 38·5% of such cases by James (1948 ; 1954). Davies and Mann (1949) and Mann (1951) showed the relation between tuberculosis and the massive fibrosis of coal pneumoconiosis radiologically. Although the organism has not been demonstrated after death in all cases of progressive massive fibrosis, many workers in this field believe that the tubercle bacillus is the chief causative agent. Experimentally, Cummins (1940) injected coal dust and quartz with and without dead tubercle bacilli intratracheally in rabbits and found that the reactions produced in the lungs by the combined action of dust and organisms were more severe

and extensive than those produced by dust alone. But the published results of biological experiments appeared to us to be not very conclusive, and it was, therefore, decided to conduct further animal experiments in order to study the effect of tubercle bacilli and dust in the lungs. Since coal dust and coal-mine dust are of great importance from the social and industrial points of view, it seemed desirable to use these ; and kaolin was also included in order to compare the results with those obtained by Kettle in his experiments in 1934.

Experiments Planned

In order to study the effect of various dusts on tuberculous infection in the lungs of animals over a long period of time, it was thought better to use a species of animal that is known to be more resistant to this infection rather than one which is more suceptible. Rats are highly resistant to tuberculosis, and they are commonly used in pneumoconiosis research. In order to compare the results with Kettle's work (1934), a parallel series of experiments was set up with guinea-pigs.

Six groups of rats and six groups of guinea-pigs were injected with the following : (1) B.C.G. (heat-killed), (2) " mine-dust ", (3) " mine-dust " + B.C.G., (4) anthracite + B.C.G., (5) kaolin, (6) kaolin + B.C.G.

Various workers have shown that anthracite coal does not produce any permanent lesions in the lungs of experimental animals, even after long periods of time, grade 1 fibrosis rarely being attained (*e.g.*, Belt and King, 1945 ; Ray, King, and Harrison, 1951 ; Wright, 1951). Therefore it was deemed unnecessary to set up a control experiment with anthracite alone. Moreover, a control experiment with " anthracite coal-mine dust " (containing some siliceous matter as well as the anthracite) was being included.

Description of Samples of Dust and Organisms

Mycobacterium tuberculosis—B.C.G.—The strain of B.C.G. was kindly supplied by Dr. H. J. Benstead, Central Public Health Laboratory, Colindale. It was from the standard Copenhagen strain, a 12-day culture on Lowenstein-Jensen's medium.

Anthracite.—This sample from South Wales was turbine ground and kindly prepared by Dr. B. M Wright. Its ash content was 2·4% and its size distribution is given in Table 1.

" Mine-dust ".—Because of the difficulty of obtaining sufficient airborne coal-mine dust it was decided to prepare a synthetic mixture of powdered coal and shale which would closely approximate coal-mine dust in composition. The sample contained 80% anthracite coal (turbine-ground as above) + 20% shale. The shale (Ammanford B) was likewise from a South Wales anthracite mine, from a seam overlying the coal measure. It contained 31% quartz, 51% mica, 6% kaolin, and 7% carbonates, and was found by Belt and King (1945) to be only minimally fibrogenic in animals.

Kaolin.—The sample originally used by Kettle in 1932 and 1934 was still available (British Drug Houses, labelled " Society of Leather Trades Chemists' Specification "). It was mostly crystalline, partly amorphous, and consisted mostly of aluminium silicate.

The size distribution and analyses of these dusts are given in Table 1. Because the shale dust was of smaller size than the anthracite, the size distribution of the mixture ("mine-dust") was slightly lower than that of the anthracite.

TABLE 1

SIZE DISTRIBUTION AND ANALYSIS OF DUSTS USED FOR INJECTIONS

Samples (Size in μ)	Anthracite		" Mine-Dust " (80% Anthracite + 20% Shale)		Kaolin	
	Per cent.		Per cent.		Per cent.	
	By No.	By Mass	By No.	By Mass	By No.	By Mass
0·16–0·23	—	—	—	—	3	0·08
0·23–0·32	—	—	—	—	18·9	1·32
0·32–0·45	—	—	19·2	0·6	38·2	7·9
0·45–0·64	—	—	16·7	1·6	16·8	9·8
0·64–0·90	37·7	1·0	25·9	6·6	12·3	20·5
0·90–1·30	14·7	1·1	24·7	17·4	9·5	43·6
1·30–1·80	11·7	2·4	8·7	17·5	1·3	16·8
1·80–2·60	16·9	9·6	3·4	19·3	—	—
2·60–3·60	9·9	15·9	0·9	14·6	—	—
3·60–5·10	6·5	29·4	0·5	22·5	—	—
5·10–7·20	0·6	33·3	—	—	—	—
7·20–10·20	0·2	7·3	—	—	—	—
Particles counted	390		863		640	
Estimated surface area ($m^2/g.$)	1·2		1·8		—	
Silica solubility (mg./100 ml.; King, 1945) ..	0·2		0·9		1·1	
Ash content (380°) (%) ..	2·4		22		99	
Composition (%)						
Coal	97·6		78		—	
Kaolin ..	1		5		77	
Mica	½		10		12	
Quartz ..	½		6		8 (hydrated silica)	
Carbonates ..	½		1		—	

Preparation of Suspensions for Injection

Myco. tuberculosis—B.C.G.—The strain of B.C.G. was sub-cultured on glycerine nutrient agar medium. A fine granular suspension of the organisms was killed by autoclaving for 20 min. at 13 lb. pressure. (Sterility tests in Lowenstein-Jensen medium ensured the effectiveness of autoclaving.) Just before the injections were made this was added to the various dust suspensions, or sterile physiological saline for controls, in such volumes as to make the final concentration of B.C.G. 2 mg./ml. of suspension when introduced into the lungs of the experimental animals.

Dust Suspensions.—Of each of the dusts (anthracite, "mine-dust", and kaolin), 2·5 g. was weighed into 4 oz. screw-cap bottles. Cream-free milk (about 3%) was added to help to keep the particles in suspension. Sterile physiological saline was then added to the bottles so that the suspension contained 100 mg. of dust per ml. The bottles were then sterilized by autoclaving (20 min. at 15 lb. pressure).

To those suspensions which were to be injected in combination with killed B.C.G. the previously sterilized B.C.G. suspension was added and intimately mixed immediately before the injections were made. The volume of B.C.G. suspension added was calculated to a concentration of 2 mg. B.C.G./ml. of the final mixture. Thus the individual suspensions contained 100 mg. of the particular dust and/or 2 mg. of B.C.G. per ml.

The dose of dust and organisms injected varied in rats and guinea-pigs, depending on their body weight, and was as follows :—

Body Weight of Animal (g.)	Volume of Suspension (ml.)	Amount of Dust (mg.)	Amount of B.C.G. (mg.)
200	0·5	50	1·0
300	0·75	75	1·5
400	1·0	100	2·0
500	1·25	125	2·5
600	1·50	150	3·0
700	1·75	175	3·5
800 and over	2·0	200	4·0

Animals

Twenty rats were used in each of the six groups. They were all of the male sex and were from the black-and-white hooded variety of the Medical Research Council strain. Their average weight was 300 g.

Eight guinea-pigs, four male and four female, were used in each of the six groups of experiments. Their body weights varied from 300 to 800 g. : they were equally distributed in all the groups.

Experimental Procedure

The anaesthetized animals (ether) were injected by the intratracheal route *via* the mouth (Kettle and Hilton, 1932 ; modified by King, Mohanty, Harrison, and Nagelschmidt, 1953). No dust was regurgitated. No immediate post-operative deaths occurred in any of the groups.

Duration of Experiments

The experimental animals were killed at monthly intervals in the case of rats and the experiments extended up to a period of 500 days ; guinea-pigs at longer intervals to 365 days.

Histopathological Technique

Routine necropsies were carried out on all the animals which were killed at regular intervals, as well as on any that were found dead. The lungs were fixed in 10% formol-saline and blocks taken along their long axes through the hilum to include the hilar lymph glands. The blocks were then treated with fresh fixative, dehydrated, impregnated with paraffin wax, embedded, and sectioned at 5 μ.

Serial sections were stained by Gordon and Sweets' (1936) silver impregnation, with haematoxylin and eosin, and with Van Gieson's stain. In addition, the sections from the lungs of animals which had been injected with B.C.G. were stained with Ziehl-Neelsen's carbol-fuchsin, and also with phenol auramine and the sections examined under fluorescent light in order to study the distribution of the organisms in the lesions.

Pathological Findings

Sections from the lungs were studied microscopically, and the fibrosis seen in the most advanced lesions in each case was graded according to Belt and King (1945). The five grades of fibrosis recognized are as follows : grade 1, loose reticulin fibrils, no collagen ; grade 2, compact reticulin, with or without some collagen ; grade 3, somewhat cellular, but made up mostly of collagen ; grade 4, completely acellular and fully collagenous ; grade 5, acellular, confluent collagenous.

The pathological gradings obtained, together with the number of days of survival of the animals and their mode of death, are summarized in Tables 2 and 3.

The macroscopic and microscopic appearances in the two species of animals were very similar, except in the case of the animals which had been given kaolin + killed B.C.G., where, histologically,

TABLE 2

ASSESSMENT OF FIBROSIS IN SECTIONS OF LUNGS OF RATS AFTER INTRATRACHEAL INJECTION OF DIFFERENT DUSTS, ORGANISMS, OR BOTH

Days of Survival	B.C.G.		" Mine-dust "		" Mine-dust " + B.C.G.		Anthracite + B.C.G.		Kaolin		Kaolin + B.C.G.	
	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis
30	Killed*	1 min.	Killed*	0	Killed* Died	1 —	Killed*	1	Killed*	1 min.	Killed*	1
60	Killed	1 min.	Killed	0	Killed	1	Killed	1	Killed	1 min.	Killed	1
90	Killed	1 min.	Killed Died	0 —	Killed	1	Killed	1	Killed	1 min.	Killed	1
120	Killed	1 min.	Killed	0	Killed	1	Killed	1	Killed	1 min.	Killed	1
150	Killed*	1 min.	Killed Died	0 —	Killed	1	Killed	1	Killed	1 min.	Killed	1 max.
180	Killed	1 min.	Killed*	0	Killed*	2 min.	Killed	1 max.	Killed*	1 min.	Killed*	3 max.
210	Killed (2)	1 min.	Killed (2)	0	Killed (2)	2 min.	Killed (2)	1 max.	Killed (2)	1 min.	Killed (2)	3
240	Killed	1 min.	Killed	0	Died Killed	— 2 min.	Died Killed*	— 2 max.	— Killed	— 1 min.	— Killed	— 2
270	Killed (2)	1 min.	Killed (2)	0	Killed (2)	2 min.	Killed (2)	2 max.	Killed (2)	1 min.	Killed (2)	2
300	Killed* Died	1 min. —	Killed	0	Killed	2 min.	Killed	2	Killed	1 min.	Killed	2
330	Killed	1 min.	Killed	0	Killed	2 min.	Killed	2	Killed	1 min.	Killed	2
365	Killed	1 min.	Killed	0	Killed*	2 max.	Killed	2	Killed	1 min.	Killed	2
400	Killed	1 min.	Killed	0	Killed	1	Killed Died	1 —	Killed Died (2)	1 min. —	Killed	1 min.
450	Killed	1 min.	Killed	0	Killed	1	Killed	1	Killed	1 min.	Killed	1 min.
477	—	—	—	—	Died*	1 min.	—	—	—	—	—	—
500	Killed (2)	1 min.	Killed* Died	1 —	—	—	Killed* Killed	1 1 min.	Killed (3) Killed*	1 min. 1 min.	Killed (2) Killed*	1 min. 1 min.

TABLE 3

ASSESSMENT OF FIBROSIS IN SECTIONS OF LUNGS OF GUINEA-PIGS AFTER INTRATRACHEAL INJECTION OF DIFFERENT DUSTS, ORGANISMS, OR BOTH

Days of Survival	B.C.G.		" Mine-dust "		" Mine-dust " + B.C.G.		Anthracite + B.C.G.		Kaolin		Kaolin + B.C.G.	
	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis	Mode of Death	Grade of Fibrosis
30	Killed*	1 min.	Killed* Dead	0 —	Killed*	1	Killed*	1	Killed*	1 min.	Killed* Dead	1 max. —
90	Killed	1 min.	Killed	0	Killed	1	Killed	1	Killed	1 min.	Killed	1 max.
120	Killed	1 min.	Killed	0	Killed	1 max.	Killed	1	Killed	1 min.	Killed	1 max.
180	Killed*	1 min.	Killed	0	Killed	2 min.	Killed	2 min.	Killed	1	Killed*	2 max.
240	Killed	1 min.	Killed*	0	Killed*	2 max.	Killed*	2 max.	Killed*	1	Killed	2
300	Killed	1 min.	Killed	0	Killed	2	Killed Dead	2 min. —	Killed (2)	1	Killed	2
365	Killed*	1 min.	Killed*	0	Killed*	1 min.	Killed*	1	Killed*	1	Killed*	1
500	Killed	0	—	—	Killed	1 min.	—	—	—	—	—	—

*Sections from these animals are reproduced in the figures.
Max. = maximal; min. = minimal within the indicated grade of fibrosis.
Numbers in brackets indicate the numbers of animals killed or found dead.

the reaction in rats seemed to be slightly more marked than that in guinea-pigs.

Macroscopic Appearance in Rats and Guinea-pigs

Macroscopically there was no difference between the lungs of rats and guinea-pigs in the various series, and they are described together. The lesions appeared somewhat larger in the groups of animals which received dust and organisms than in those which had the dust or the organisms alone.

B.C.G.—Evenly distributed, discrete, whitish lesions, 1 to 2 mm. in diameter, were seen in the lungs from 30 days onwards. They were slightly larger at 240 days, being about 4 mm. in diameter ; later they diminished in size and number and at 500 days they were small and scanty.

" Mine-dust ".—In both rats' and guinea-pigs' lungs the dust was distributed diffusely. In some cases, subpleural collections of dust were seen on the dorsal aspects of the lungs.

" Mine-dust " + B.C.G.—On the lung surfaces there were collections of dust, around which in the early stages were greyish lesions about 1 to 2 mm. in diameter. These lesions increased in size during the course of the experiment and persisted till its end at 500 days.

Anthracite + B.C.G.—The appearances were very similar to those found in the lungs of animals receiving " mine-dust " + B.C.G.

Kaolin.—Small, whitish collections of dust were seen distributed diffusely throughout the lungs of both rats and guinea-pigs. There was no change in the macroscopic appearance throughout the experiment.

Kaolin + B.C.G.—From 30 days onwards there were white areas over the lung surfaces which were larger than those seen in the previous group. From about 210 days there were definite firm, white areas on the lungs, resembling fibrosis. Later still, towards the termination of the experiment, the appearances were very similar to those seen with kaolin alone, except that the lesions were larger.

The tracheo-bronchial lymph nodes were enlarged to several times the normal in all these groups, and were black in animals receiving coal.

Microscopic Appearances

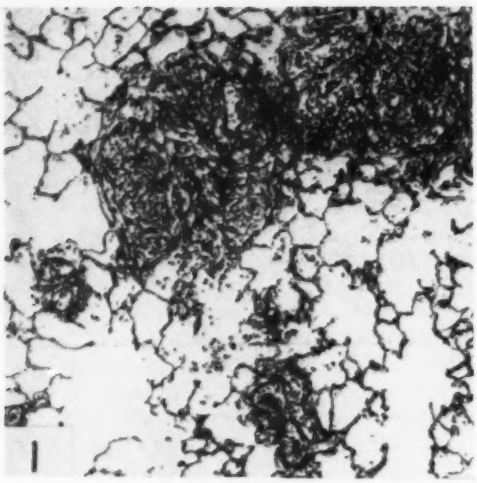
The histological lesions in the lungs of rats and guinea-pigs in the various groups of experiments were very similar in the type of reaction. " Mine-dust " did not produce any fibrosis in either rats or guinea-pigs ; B.C.G. alone and kaolin alone produced mild fibrosis (grade 1) ; while " mine-dust " + B.C.G., anthracite + B.C.G., and kaolin + B.C.G. produced well marked fibrosis (grades 2 and 3 respectively in rats and grade 2 in guinea-pigs). The lesions reached a maximum at about the same period in all cases and then decreased in severity towards the end of the experiments. The demonstration of acid-fast organisms in the case of guinea-pigs was difficult ; they were seen in animals killed early in the experiment, but only in small numbers, or not at all, during the last 100 to 150 days.

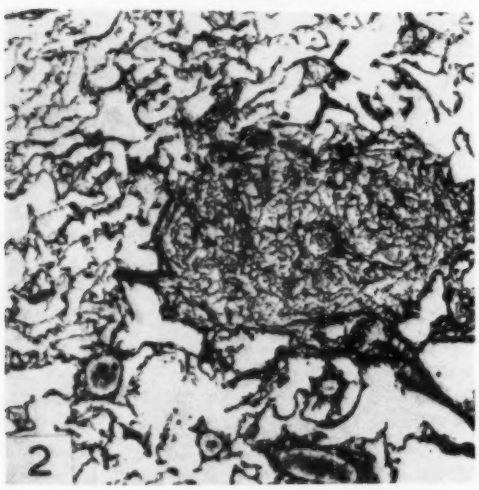
Rats

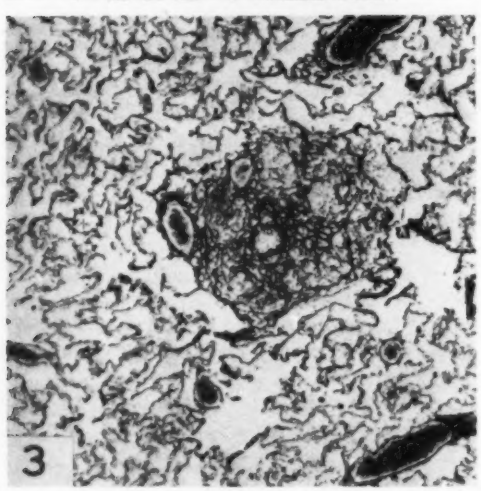
B.C.G.—At 30 days there were many nodular lesions, about 100 to 200 μ in diameter, throughout the lung fields. They were composed mainly of mononuclear cells with some bacilli in the centre. On reticulin staining there appeared to be a loose network of fine reticulin fibres within these nodular lesions (grade 1 fibrosis, Fig. 1). Thereafter, the lesions showed a slight increase in size (200 to 300 μ) but there was no evidence of increase in reticulin up to 150 days (Fig. 2). After this period there appeared to be a diminution in the size of the lesions (100 to 150 μ). The fibrosis still remained the same as at first and at 300 days was grade 1 (Fig. 3). From this time onwards the lesions seemed to be reduced, both in size and in number, and at 500 days only an occasional small cellular lesion could be seen. Acid-fast bacilli were, however, demonstrable in such lesions, although they were reduced in number compared with the earlier stages.

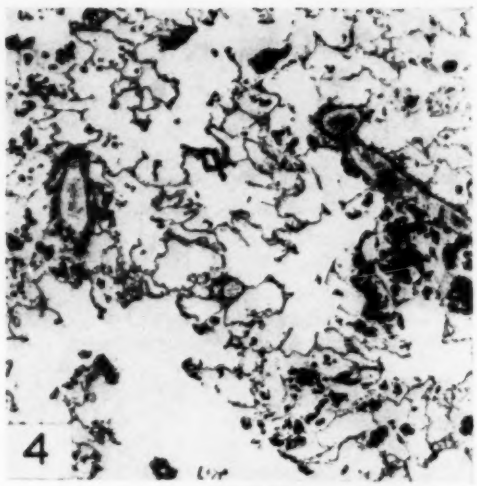
" Mine-dust ".—In the early stages the dust appeared to be distributed diffusely throughout both lungs. At 30 days there were plenty of dust particles lying free within the alveoli. In some areas, dust cells were collected into small aggregations but there was no evidence of fibrosis (Fig. 4). Between this time and 180 days the dust cells began to collect into definite nodules, leaving the intervening lung clear. At 180 days the dust cell collections had enlarged to a certain extent, without the appearance of any fibrosis (Fig. 5). Between 180 days and the termination of the experiment at 500 days, the dust appeared to become more tightly packed together into focal aggregations with just enough reticulin fibres around them to hold the dust together. There was no further fibrosis (Fig. 6).

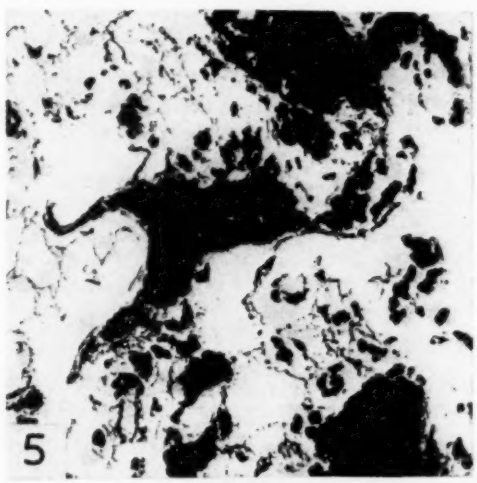
" Mine-dust " + B.C.G.—At 30 days there were some dust cells lying free within the lung alveoli,

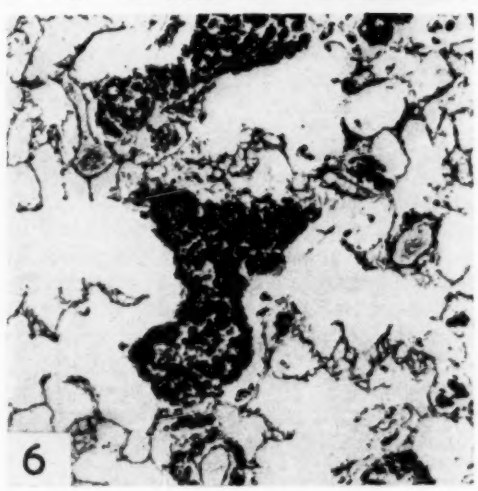












Rat lungs after the injection of 1·5 *mg. of dead B.C.G. Silver impregnation* (80).

FIG. 1.—30 days. Nodular lesions. Loose network of reticulin fibres. Grade 1 fibrosis.

FIG. 2.—150 days. Nodular lesion with loosely woven reticulin fibres. Grade 1 fibrosis.

FIG. 3.—300 days. Small nodular lesion with loose reticulin network. Grade 1 fibrosis.

Injection of 75 *mg. of "mine-dust". Silver impregnation* (60).

FIG. 4.—30 days. Diffuse distribution of dust particles with an occasional small aggregation. No fibrosis.

FIG. 5.—180 days. Dust collected into dense aggregations without any fibrosis.

FIG. 6.—500 days. Dust tightly packed into focal aggregations with a few reticulin fibres around them, but no fibrosis.

while others were aggregated to form nodular lesions. These lesions were composed of dust cells together with many epitheloid cells and some acid-fast organisms, and seemed to be due to the combined action of the dust and organisms (Fig. 7). Within such lesions were loosely arranged fine reticulin fibres (grade 1 fibrosis ; Fig. 8). By 120 days the lesions had increased in size, but there was very little increase in fibrosis, the lesions remaining within the maximum limits of grade 1 fibrosis. At 180 days, they appeared to have advanced and the reticulin fibres were thicker and becoming compact (grade 2 fibrosis, minimal ; Fig. 9). No further progress was noted in the lesions till 365 days, when the reticulin appeared to be very thick and compact (grade 2 fibrosis, maximal ; Fig. 10). After this the lesions gradually diminished in number and severity. The nodules were smaller and the reticulin fibres, which had been thick and compact earlier, were finer and loosely arranged and, near the end of the experiment (477 days) only a few small nodules were seen. At this stage a few collections of dust with mild thickening of the alveolar walls were seen but no definite fibrosis (Fig. 11).

With fluorescent light the microscopic preparations examined for organisms showed about eight in an area of $2 \times \frac{3}{4}$ cm. of lung at the period when the fibrosis was at its maximum, and two only in the same area, approximately, at 500 days.

Anthracite + B.C.G.—The lesions produced by anthracite coal and B.C.G. in the lungs of rats were very similar to those produced by " mine-dust " and B.C.G. In the early stages (30 days) there were cellular lesions composed mainly of epitheloid cells, dust cells, and acid-fast organisms (Fig. 12). Within these lesions there was a slight increase of reticulin fibres (grade 1 fibrosis, minimal ; Fig. 13). The lesions remained unchanged till 150 days, when there was thickening of the reticulin fibres in them and the fibrosis reached a fully developed grade 1. By 240 days the cellular lesions were larger, more numerous, and showed thick and compact reticulin (grade 2 fibrosis, maximal ; Fig. 14). There was no appreciable change from this time till 400 days. At this stage the lesions were somewhat smaller and less numerous, and at 500 days there were only scattered lesions with a few reticulin fibres (grade 1 fibrosis ; Fig. 15).

Examination of sections stained with auramine revealed under fluorescent light about eight bacilli in an area $2 \times \frac{1}{2}$ cm. of lung tissue at 180 days, and only three bacilli in an area 3×1 cm. at 300 days.

Kaolin.—At 30 days this dust produced a diffuse exudative reaction with numerous giant cells containing dust particles. The cells tended to collect together but did not form compact nodules. A few fine reticulin fibres were seen within these collections (grade 1 fibrosis, minimal ; Fig. 16). The lesions did not appear to progress and the fibrosis still remained grade 1 minimal (Figs. 17 and 18).

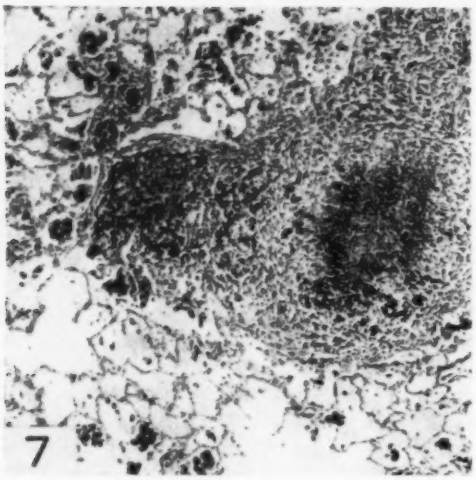
Kaolin + B.C.G.—The lesions resulting from the introduction of kaolin dust and B.C.G. were very different from those produced by the dust alone. At 30 days there was the same diffuse infiltration of the lungs, with large numbers of giant cells containing engulfed dust particles and collected together in some areas to form nodules, within which were acid-fast organisms and loose reticulin fibres (grade 1 fibrosis ; Fig. 19). With the advance of time, however, the lesions showed a definite increase of reticulin. There was generalized thickening of the alveolar walls, and at 180 days portions of the lung showed some consolidation due to dust-laden cells. Some bacilli were demonstrable in these areas, and there were many thick compact bundles of collagen fibres (grade 3 fibrosis ; Fig. 20). The fibrosis remained at this stage till 270 days, when the lesions began to show signs of regressing, and at 500 days there were only a few nodular lesions present together with mononuclear cells distributed throughout the lungs and some alveolar fibrosis in the form of a reticular network (Fig. 21).

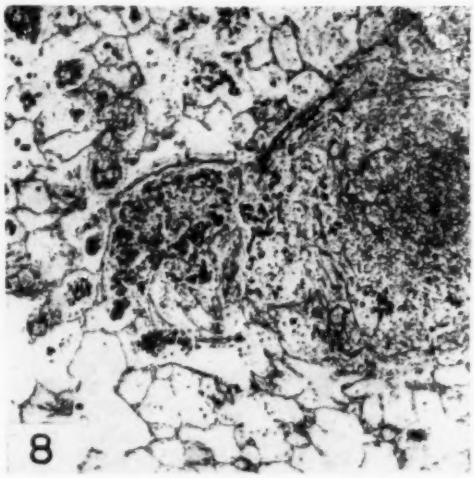
Auramine-stained sections examined with fluorescent light revealed about seven bacilli in an area $2 \times \frac{1}{2}$ cm. of lung tissue at the period when the fibrosis was most marked, and only about three bacilli in an area 3×1 cm. at the end of the experiment.

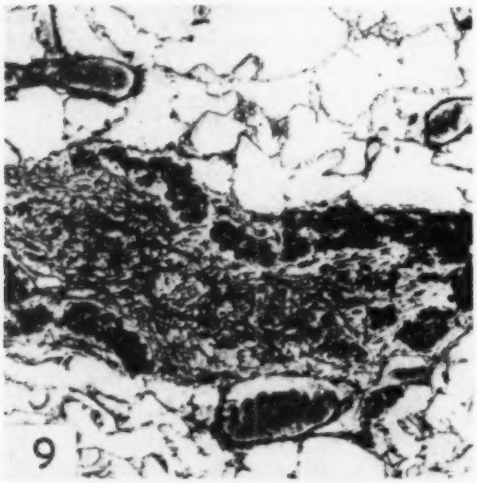
Guinea-pigs

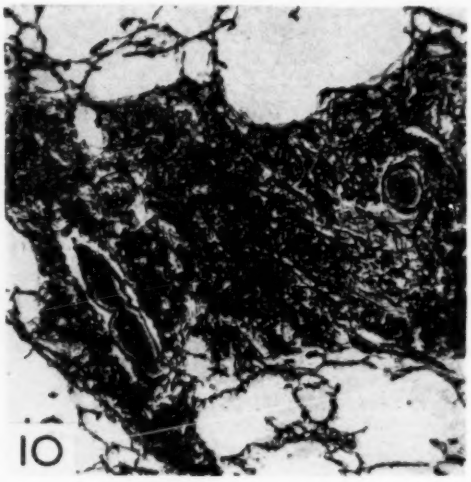
The histological lesions produced by dust, organisms, and the combined action of the two in the lungs of guinea-pigs were similar to those produced in the lungs of rats by the same agents. The different degrees of susceptiblity of the two animal species to the infecting organism did not seem to affect the lesions.

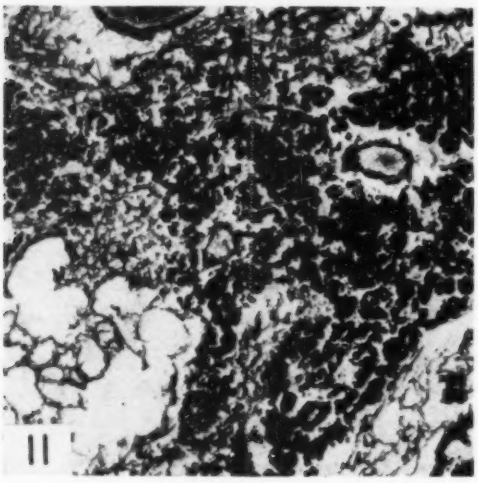
B.C.G.—At 30 days there were numerous cellular lesions about 100 to 200 μ in diameter. A few fine, loosely arranged reticulin fibres were seen in some of the lesions (grade 1 fibrosis, minimal ; Fig. 22). Within the next six months the lesions enlarged to 200 to 300 μ, and at 180 days there was no visible increase in the reticulin fibres within the











Rat lungs after the injection of 75 mg. of "mine-dust" and 1·5 mg. of dead B.C.G.

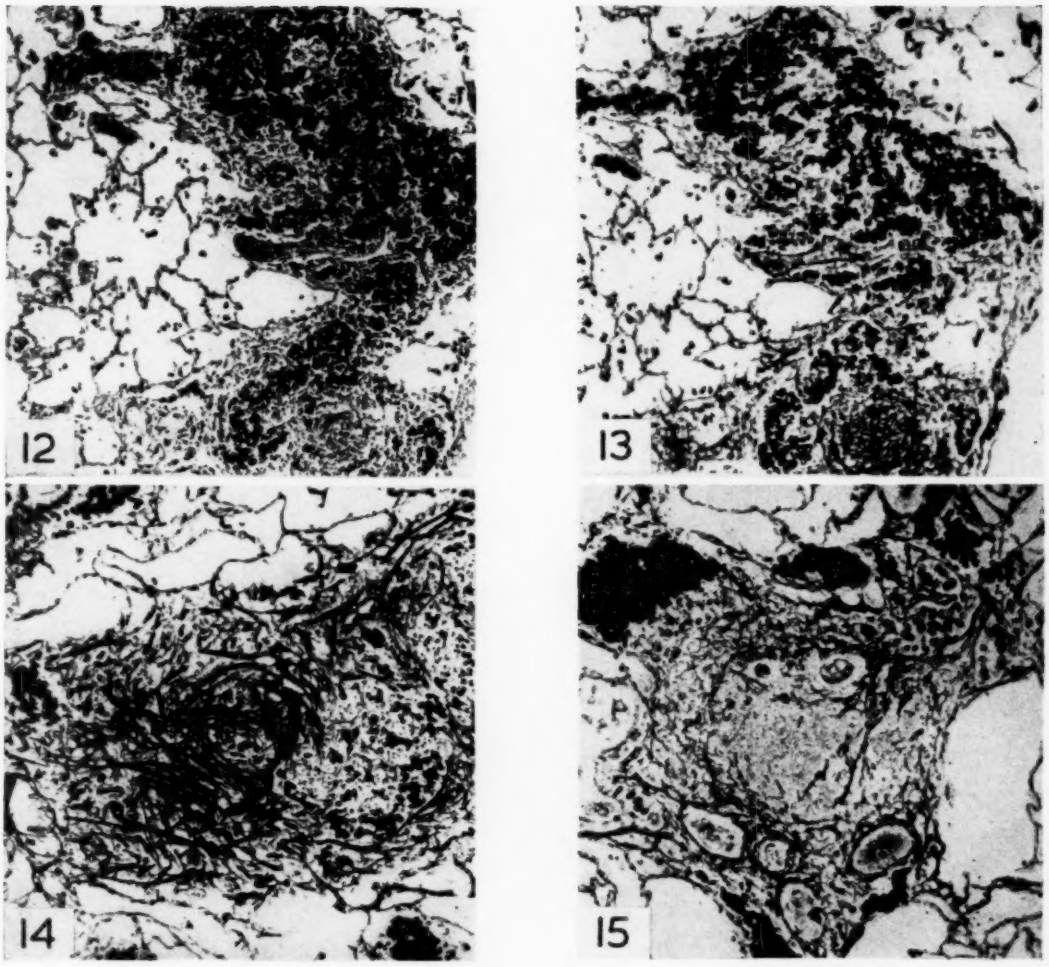
FIG. 7.—30 days. Nodular lesion composed of dust cells with epitheloid cells, due to the combined action of dust and organisms. Haematoxylin and eosin (55).

FIG. 8.—30 days. Same area as Fig. 7. Combined dust and infective lesion with loose network of fine reticulin fibrosis. Grade 1 fibrosis. Silver impregnation (60).

FIG. 9.—180 days. Combined dust and infective lesion with thick reticulin fibres. Grade 2 fibrosis, minimal. Silver impregnation. (80).

FIG. 10.—365 days. Combined dust and infective lesion with thick compact reticulin fibres. Grade 2 fibrosis, maximal. Silver impregnation (80).

FIG. 11.—477 days. Collections of dust with mild thickening of the surrounding alveolar walls, but no fibrosis. Silver impregnation. (80).



Rat lungs after the injection of 75 mg. of anthracite coal and 1·5 mg. of dead B.C.G.

FIG. 12.—30 days. Nodular lesions composed mainly of dust cells and epitheloid cells due to the combined action of dust and organisms. Haematoxylin and eosin (60).

FIG. 13.—30 days. Same area as Fig. 12. Combined dust and infective lesions with a few fine reticulin fibres. Grade 1 fibrosis, minimal. Silver impregnation (80).

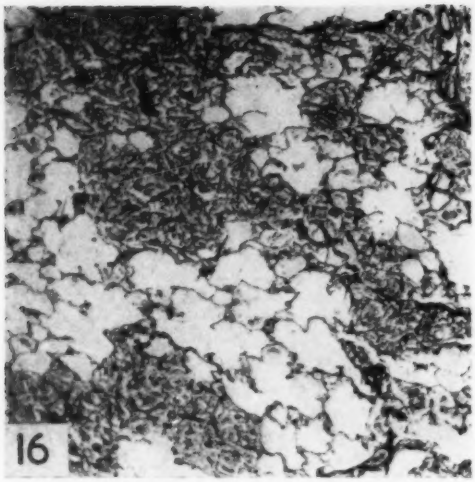
FIG. 14.—240 days. Nodular lesions, due to dust and organisms, showing thick and compact reticulin. Grade 2 fibrosis, maximal. Silver (80).

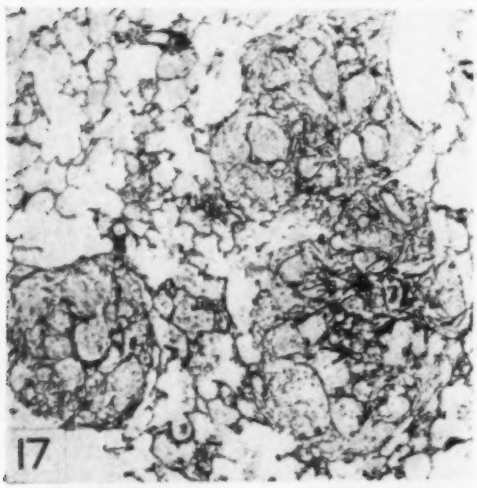
FIG. 15.—500 days. Combined dust and infective lesion, much less severe than at 240 days, showing a few fine reticulin fibres. Grade 1 fibrosis. Silver (80).

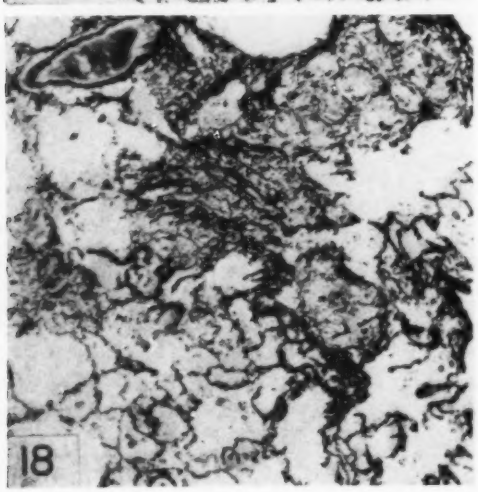
lesions (Fig. 23). From this time onwards they diminished in size (100 to 200 μ) and at 365 days were seen as small cellular areas with a few reticulin fibres (Fig. 24). They persisted even up to 500 days although they were few and small.

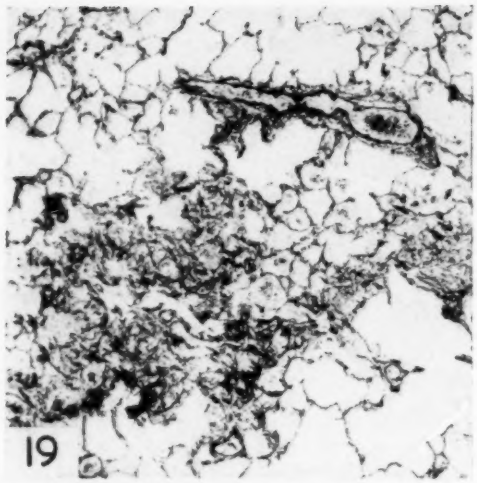
"Mine-dust".—Numerous dust particles were seen distributed diffusely throughout the lung fields within the alveoli and in the interstitial tissue at 30 days (Fig. 25). By 150 days dust cells had aggregated to form irregular nodules. There was no development of reticulin fibres within such nodules (Fig. 26). At 365 days the dust collections appeared compact but there was no fibrosis at all (Fig. 27).

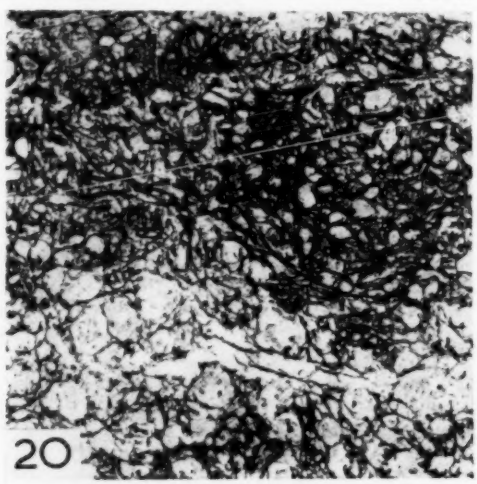
"Mine-dust" + B.C.G.—At 30 days there were small nodular lesions composed of dust cells and epitheloid cells together with a loose network of fine reticulin fibres in them (grade 1 fibrosis ;

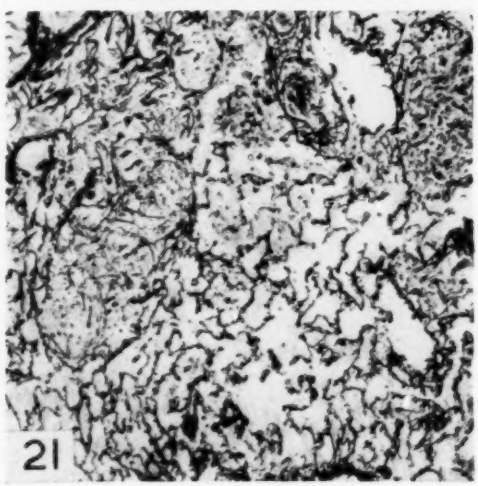












Rat lungs after the injection of 75 mg. of kaolin dust. Silver impregnation (60).

FIG. 16.—30 days. Commencing aggregation of dust particles. (Diffuse exudative reaction with numerous dust-containing giant cells.) A few fine reticulin fibres within the aggregations. Grade 1 fibrosis, minimal.

FIG. 17.—180 days. Nodular collections (of dust-containing giant cells). A few reticulin fibres arranged loosely within the nodules. Grade 1 fibrosis, minimal.

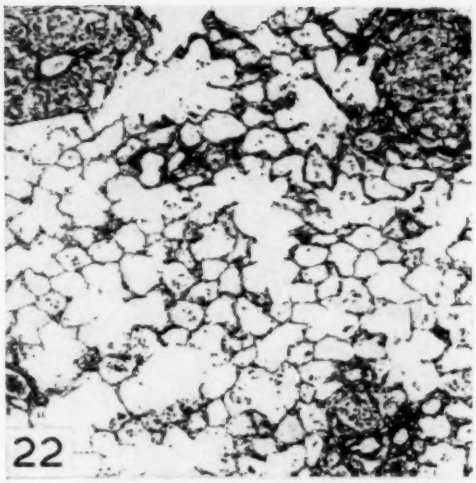
FIG. 18.—500 days. Nodular lesions with loose reticulin network. Grade 1 fibrosis, minimal.

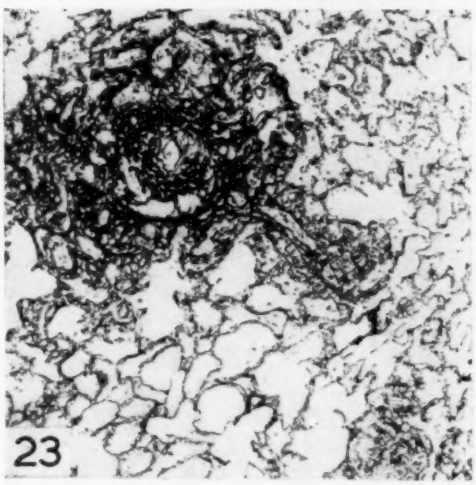
Injection of 75 mg. of kaolin dust and 1·5 mg. of dead B.C.G. Silver impregnation.

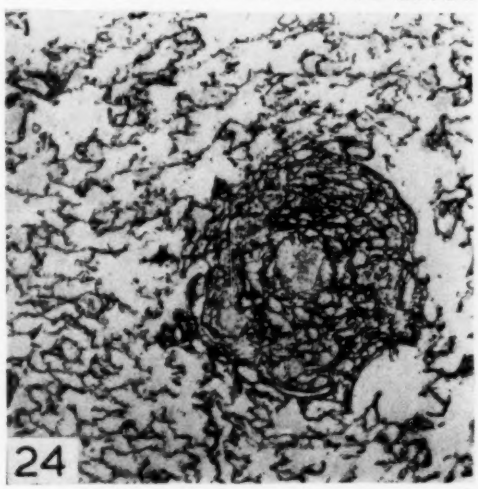
FIG. 19.—30 days. Combined dust and infective lesions with loose network of reticulin fibres. Grade 1 fibrosis (60).

FIG. 20.—180 days. Diffuse lesions, due to the combined action of dust and organisms, with thick and compact collagen (grade 3 fibrosis). Generalized thickening of alveolar walls in the neighbourhood of the lesions (65).

FIG. 21.—500 days. Few reticulin fibres within nodules and some alveolar fibrosis in the form of a reticular network. Reaction much milder than at 180 days (70).





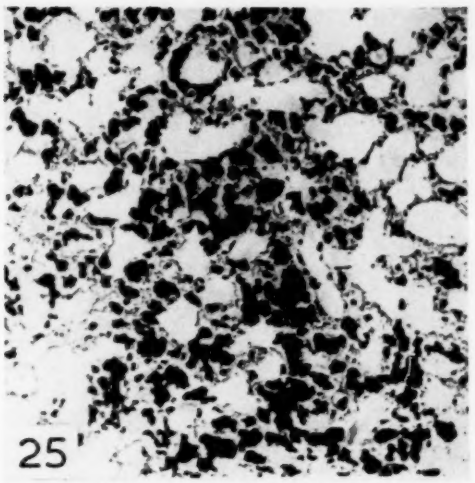


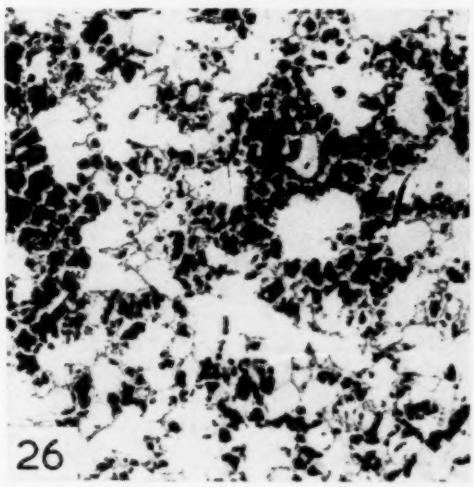
Guinea-pig lungs after the injection of 3 mg. of dead B.C.G. Silver impregnation (60).

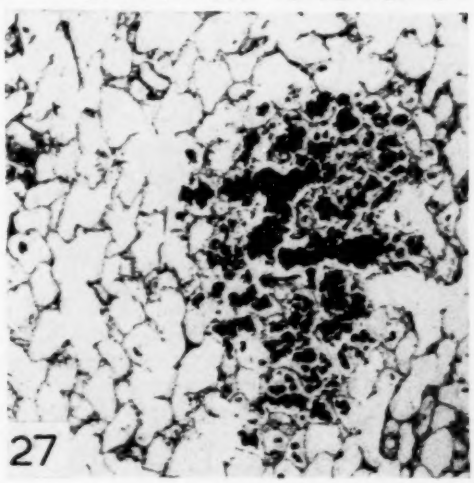
FIG. 22.—30 days. Nodular lesions with a few fine reticulin fibres. Grade 1 fibrosis, minimal.

FIG. 23.—180 days. Nodular lesions with a loose reticulin network. Grade 1 fibrosis.

FIG. 24.—365 days. Cellular lesions, smaller in size than at 180 days, and with a few fine reticulin fibres. Grade 1 fibrosis.







Injection of 150 *mg. of "mine-dust". Silver impregnation* (60).

FIG. 25.—30 days. Dust diffusely distributed throughout lungs. No evidence of increased reticulin.

FIG. 26.—240 days. Small collections of dust in irregular nodules, without any fibrosis.

FIG. 27.—365 days. Dust collected into compact nodules with scanty reticulin fibres, but no definite fibrosis.

Fig. 28). The lesions progressed, and by 240 days the nodules had enlarged and the reticulin fibres were thick and compact, with a small amount of collagen (grade 2 fibrosis ; Fig. 29). From this time till 300 days there was no progress, and after that the lesions seemed to regress ; by 365 days there were only a few cellular collections with scanty reticulin fibres (grade 1 fibrosis, subminimal ; Fig. 30), and at 500 days the picture was no different.

Anthracite + B.C.G.—Histologically the lesions were similar to those seen in the previous group. At 30 days there were small focal accumulations of dust cells and epitheloid cells in the form of nodules (Fig. 31), which contained a loose network of reticulin fibres (grade 1 fibrosis). At 180 days there were many, some of them with grade 2 fibrosis (minimal). By 240 days the nodules were larger and the reticulin fibres compact, with some collagen (grade 2 fibrosis, maximal ; Fig. 32). After this the lesions gradually diminished in size and at 365 days there were only a few with some reticulin fibres in them (Fig. 33).

Kaolin.—At 30 days a large number of foreign-body giant cells containing dust particles were seen distributed throughout the lung fields (Fig. 34). A loose reticulin network was demonstrable in some of these areas, as well as among localized collections of giant cells (grade 1 fibrosis, minimal ; Fig. 34). From this period up to 240 days there was very little change in the lesions, with the exception of a slight increase in reticulin fibres (Fig. 35). The lesions were, on the whole, diffuse, and remained so from the beginning of the experiment to its termination at 365 days (grade 1 fibrosis ; Fig. 36).

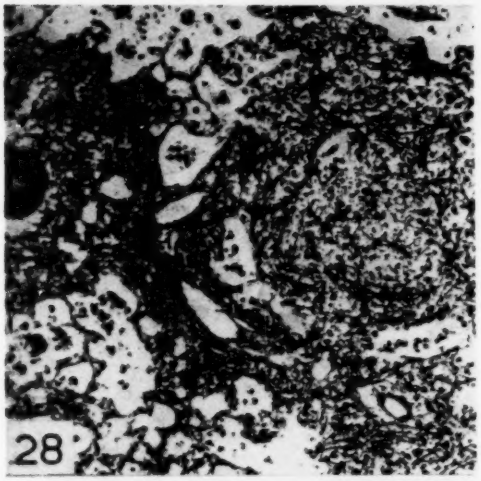
Kaolin + B.C.G.—At 30 days there were large portions of the lung packed with giant cells containing dust particles. In certain areas there were nodular lesions composed of these giant cells, mononuclears, and epitheloid cells. Some fine strands of reticulin were seen in the affected parts of the lung (grade 1 fibrosis ; Fig. 37). During the next five months the lesions advanced in severity and the histological appearances were markedly different in every respect from those produced by kaolin alone at the same period of time. Areas of necrosis were seen in some of the lesions and parts of the lung were solid with dust cells. By 180 days there was coarse reticular fibrosis of the alveolar walls in the affected regions and thick compact reticulin, together with some collagen within the actual lesions (grade 2 fibrosis, maximum ; Fig. 38) whereas in the lesions produced by kaolin alone at this same period there was nothing more than a fine network of reticulin. Thereafter, the lesions decreased in severity, and at 365 days only a few fine reticulin fibres remained together with some mild alveolar fibrosis (Fig. 39).

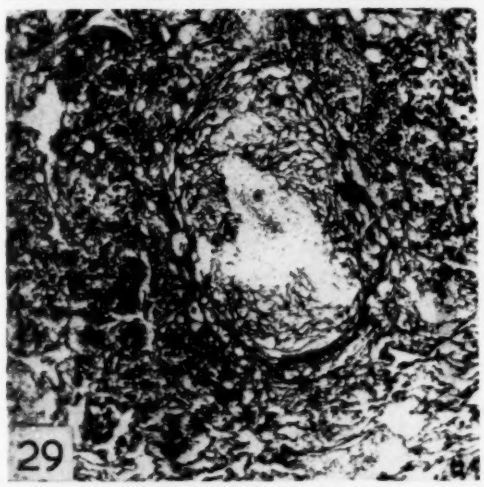
Discussion

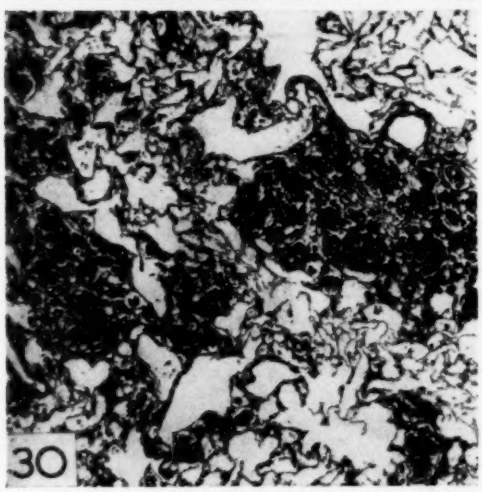
It is apparent from the foregoing results that the influence of anthracite, " mine-dust ", and kaolin on avirulent tuberculous " infection " * produced by dead B.C.G. in the lungs of rats and guinea-pigs is such that the lesions are aggravated by them. The combined action of any one of the dusts and dead B.C.G. produced more marked lesions in the lungs than any of these substances alone in the same period of time. " Mine-dust " did not produce any permanent pulmonary lesions, and kaolin and B.C.G. alone produced mild reticulinosis only, while the combination of anthracite dust or " mine-dust " with B.C.G. produced definite fibrotic lesions (grade 2) and kaolin and B.C.G. together produced collagenous lesions of grade 3 severity. Dust and dead tubercle bacilli influence each other in such a way that one enhances the lesions produced by the other. There were small differences in the size distributions of the dusts used, but these appeared to have little or no effect on the results produced.

A striking feature in all the experiments where dust and organisms were injected simultaneously is the regularity with which the severe reactions present in the lungs at one stage gradually disappeared during the later stages of the experiment. In all cases the lesions became more pronounced during the mid-period of the experiment and the maximum fibrosis was noted between 180 and 240 days, after which the lesions showed signs of regression till, at the termination of the experiment at 365 or 500 days, no fibrosis was evident. It would seem from these findings that fibrous tissue is capable of undergoing partial resolution spontaneously in certain cases. Collagen fibres which were plentiful at the peak period when the fibrosis was at the maximum were no longer found in any of the lesions examined in the later stages of the experiment. The fact that this was repeatedly found in every experiment involving the use of dust and organisms together is of significance and cannot be dismissed as a chance occurrence. It is not possible to offer a wholly satisfactory explanation for this partial resolution. It may be due to the disappearance of one of the stimuli which were in

* " Infection " is usually employed in connexion with invasion by living organisms. It is used here because of lack of a better term. Living bacilli are being used in present experiments to be described in a future paper.





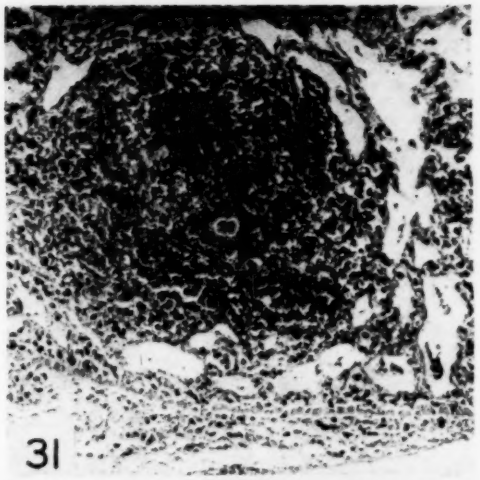


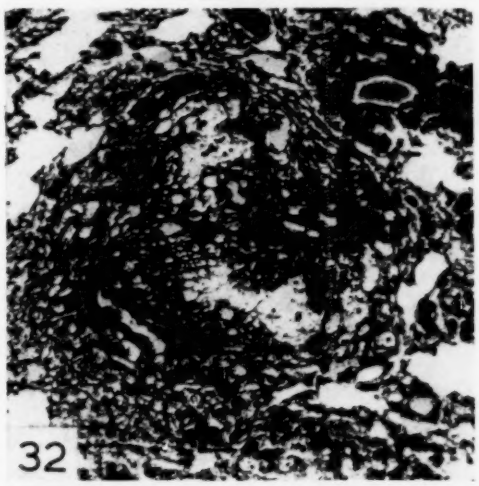
Guinea-pig lungs after the injection of 150 *mg. of "mine-dust" and* 3 *mg. of dead B.C.G. Silver impregnation* (60).

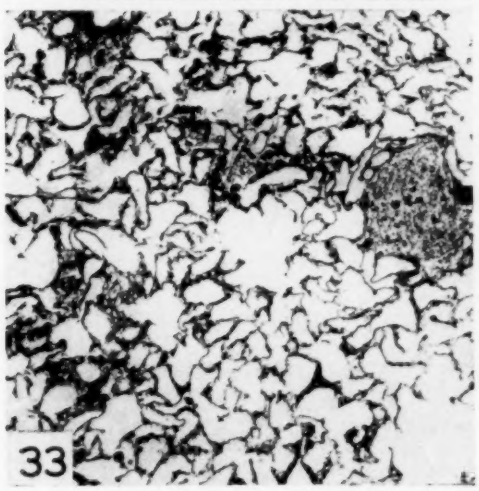
FIG. 28.—30 days. Nodular lesions with fine reticulin fibres. Grade 1 fibrosis.

FIG. 29.—240 days. Combined dust and infective lesions with thick and compact reticulin fibres and some collagen. Grade 2 fibrosis.

FIG. 30.—365 days. Nodular lesions, due to dust and infection with only a few reticulin fibres arranged loosely within them. Grade 1 fibrosis, minimal.





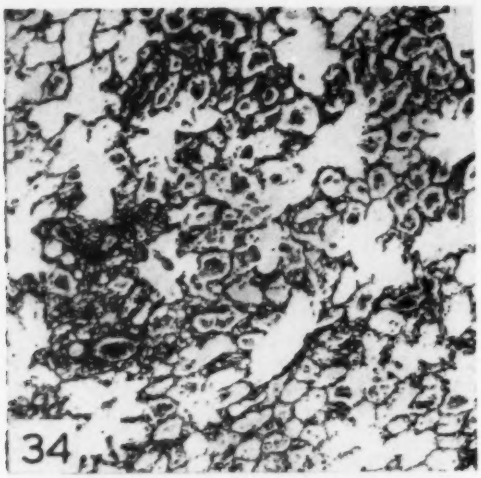


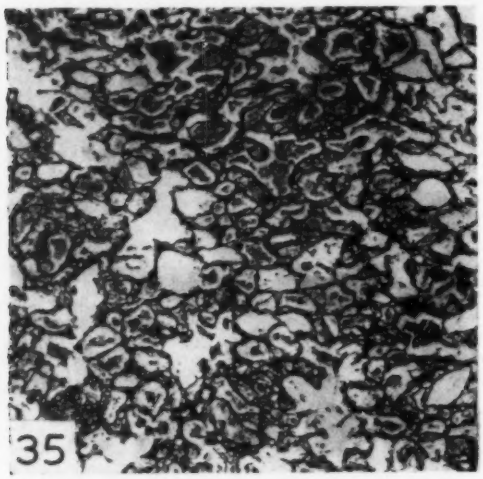
Injection of 150 *mg. of anthracite coal and* 3 *mg. of dead B.C.G.* (60).

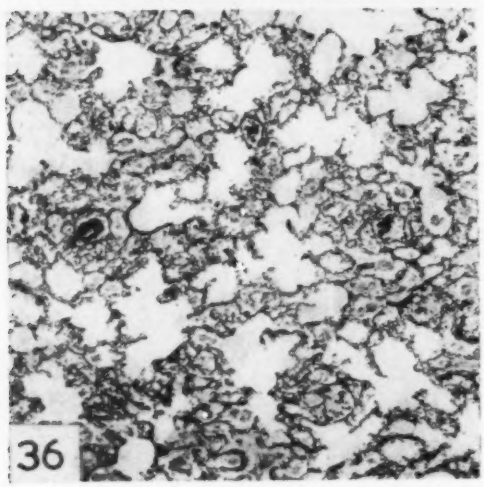
FIG. 31.—30 days. Nodular lesions produced by dust and organisms and composed of dust cells and epitheloid cells. Overlying pleura shows inflammatory thickening. Haematoxylin and eosin.

FIG. 32.—240 days. Lesions due to combined dust and organisms and composed of thick and compact reticulin fibres, together with some collagen. Grade 2 fibrosis, maximal. Silver.

FIG. 33.—365 days. Lesions much smaller and less severe than at 240 days. Only occasional reticulin fibres. Silver.





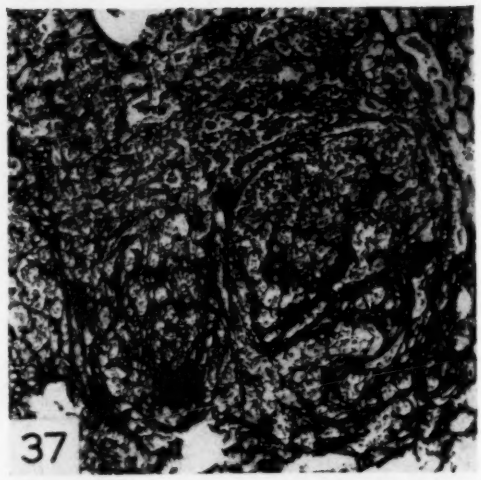


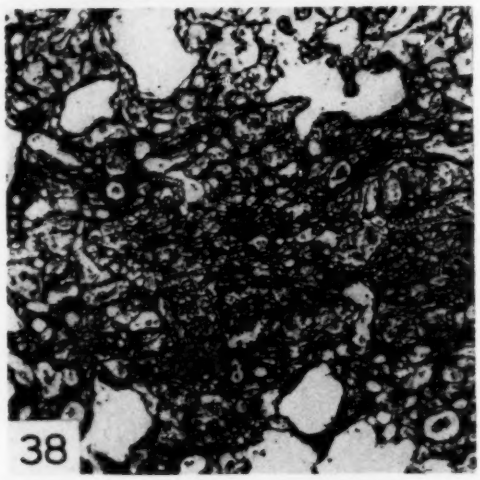
Guinea-pig lungs after the injection of 125 *mg. of kaolin. Silver impregnation* (60).

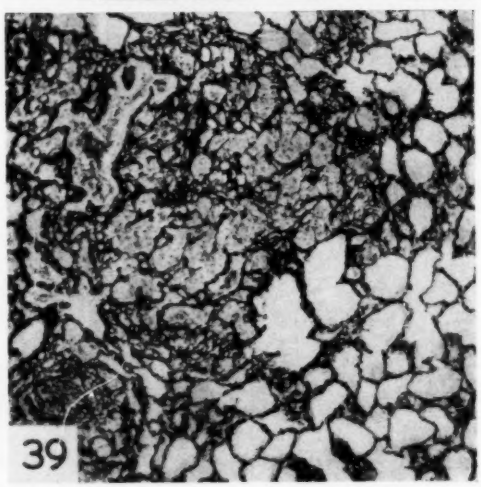
FIG. 34.—30 days. Diffuse exudative reaction with many dust-containing giant cells. Loose network of reticulin fibres among some collections of cells. Grade 1 fibrosis, minimal.

FIG. 35.—240 days. Fine reticulin fibres in giant cell collections. Grade 1 fibrosis.

FIG. 36.—365 days. No increase of reticulin in the lesions beyond that seen at 240 days. Grade 1 fibrosis.







Injection of 125 *mg. of kaolin and* 2·5 *mg. of dead B.C.G. Silver impregnation.* (60).

FIG. 37.—30 days. Large areas of lung show combined dust and infective lesions in which are loosely arranged strands of reticulin. Grade 1 fibrosis, maximal.

FIG. 38.—180 days. Lesions show numerous thick strands of reticulin arranged in compact manner. Grade 2 fibrosis, maximal. Coarse reticular fibrosis of alveolar walls in neighbourhood of lesions. Mild degree of emphysema.

FIG. 39.—365 days. Lesions less severe than at 180 days. Loose reticulin network. Grade 1 fibrosis. Mild reticulinosis of alveolar walls.

the form of dead bacilli themselves or the toxic substances which they contain. There was, in fact, some evidence that the bacilli were being removed from the lungs during the later stages of the experiment. Examinations of lesions for organisms (under fluorescent light) during the period when the fibrosis was maximum, and again when partial resolution had taken place, revealed a definite difference in the number present. Even at the time when the lesions were severe bacilli were scanty, being only about six to ten in the whole lung field examined (approximately 3 sq. cm.); but towards the end of the experiments, when partial resolution had taken place, the numbers were still further reduced, being about two to four in a lung field of approximately the same areas as before. This evidence that bacilli were disappearing from the lungs agrees with Kettle's (1934) findings. Kettle (1934) produced collagenous lesions very similar to the infective silicotic nodules seen in human beings. The maximum fibrosis was found at 112 days and was still present at 141 days. No descriptions were given of lesions beyond this period. It is possible that if his experiments with dust and organisms had been continued for a longer period results similar to ours might have been obtained, *i.e.*, partial resolution of lesions. With dead B.C.G. alone he found that the organisms "disappeared altogether in the later stages of the experiment", but no definite time is mentioned. In our experiments a very few organisms were demonstrable in rats even as late as 500 days after injection. The experiments of Cummins (1940) also were conducted up to a period of 180 days only, and it is possible that had they been continued longer the lesions might have resolved.

Summary

The influence of anthracite, "mine-dust", and kaolin on avirulent tuberculous "infection" produced by dead bacillus Calmette-Guérin (B.C.G.) in the lungs of rats and guinea-pigs has been studied by the intratracheal injection of these substances alone and in combination. The reactions produced by the combinations of the substances were similar in the two species of animals and did not seem to have been affected by their different degrees of susceptibility to tuberculosis.

Bacillus Calmette-Guérin alone produced mild lesions in rats and guinea-pigs; they appeared at 30 days and persisted till 500 days and 300 days respectively, although at this stage they were scanty and smaller in size. "Mine-dust" did not produce any pulmonary fibrosis in as long a period of time as 500 days. "Mine-dust" and B.C.G. produced definite fibrosis which reached its maximum (grade 2) at 365 days in rats and 240 days in guinea-pigs; thereafter the lesions underwent partial resolution. Anthracite dust and B.C.G. produced lesions essentially similar to the foregoing, which reached the maximum severity (grade 2) between 180 and 240 days in both species and then resolved partially. With kaolin and B.C.G. the reaction was more marked in rats than in guinea-pigs. In both, the maximum fibrosis (grade 3 and grade 2 respectively) was reached at 180 days, the lesions diminishing in severity beyond that period.

Our thanks are due to the Medical Research Council for a grant to cover the expenses of this investigation; to Messrs. B. C. S. Hollands and W. Weedon for help with the injections and care of the animals; and to Dr. John Rogan for helpful discussion and advice.

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Brit. J. industr. Med., 1954, **11**, 260.

CORONARY HEART DISEASE IN TRANSPORT WORKERS

A PROGRESS REPORT*

BY

J. N. MORRIS and P. A. B. RAFFLE

From the Social Medicine Research Unit, Medical Research Council, and the Medical Department, London Transport Executive

During 1949 and 1950 we set out to record all the cases of coronary heart disease, as they occurred and were recognized, among the drivers and male conductors aged 35 to 64 years, of the red buses, trams, and trolleybuses of London Transport Executive, and to relate these cases to the population at risk. Some 15,500 drivers and 9,500 conductors were observed for the two years (and for as long in 1951 as was necessary to complete the information about 1950). The cases were ascertained by various established means: for example, drivers and conductors who have been off sick for any period on account of disease certified as cardiac, or for more than 28 days from any cause, are routinely identified in their garages and sent for examination to the Medical Department before returning to duty. In addition, there was a special cross-check in the Central Record of Staff Statistics for the purposes of the present enquiry to ensure that all "possible", as well as definite, cases came under scrutiny in the Medical Department. It is reasonably certain that few of the relevant cases were missed, and that sufficiently accurate diagnoses were made. A copy of the death certificate was obtained for all deaths, including those that occurred without previous sickness absence.

Because in any occupation a man may retire after his first clinical "episode", or "attack" of coronary heart disease, it was necessary to concentrate on these. The rate of first attack per 1,000 men is called the "incidence" of the disease. During the two years 1949-1950, 111 first attacks were recognized and satisfied the diagnostic criteria adopted. Of these cases, 32 occurred in conductors and 79 in drivers. When age standardized rates were calculated it was found that the incidence at 35 to 64 years was 2·0 per 1,000 men per year in the conductors but 2·7 in the drivers. Moreover, the distribution of type of presentation differed in the two occupational groups. The conductors had more angina of effort, a relatively benign manifestation of the disease; 38% of their cases presented in this way compared with 13% among the drivers. On the other hand, the conductors had only half the "immediate mortality" (deaths within three days of onset of the first attack) that occurred in the drivers, 0·4 per 1,000 men compared with 0·9. There was a suggestion, also, that the disease presented at a rather later age in the conductors. When the fate of those who did not die immediately was followed to the end of the first three months of the clinical disease, the rate of coronary mortality in the conductors was again half that of the drivers, 0·2 and 0·4 respectively, making the total in the three months 0·6 per 1,000 in conductors against 1·3 in drivers.

A Three-year Follow-up

Clearly it was necessary to enquire whether the apparent advantage of the conductors continued beyond these early months of the first clinical attack. A follow-up study of those conductors and drivers who survived the first three months was therefore carried out, and we are now reporting on the next three years, covering all the men who had their first clinical attack in 1949–50. Some of the survivors are of course still working with London Transport. Others who had retired on age or medical grounds, or resigned, were traced by administrative methods—such as their continuing pensions—or by personal search. This latter was kindly undertaken by Dr. L. G. Norman, Chief Medical Officer of the Executive, as an exercise in what might be called "shoe-leather epidemiology".

Of the original 111 cases, 64 survived the first three months: 23 conductors and 41 drivers. All were traced. Up to the end of the three years' follow-up, 13 more died of coronary heart disease: four deaths occurred among the conductors and nine among the drivers. (A driver who died from another—cardiovascular—disease has been excluded from further consideration.) The standardized rate

*Presented by P. A. B. Raffle to the Association of Industrial Medical Officers at their Provincial Meeting, July, 1954.

TABLE

INCIDENCE AND MORTALITY FROM CORONARY HEART DISEASE IN DRIVERS AND MALE CONDUCTORS OF CENTRAL BUSES, TRAMS, AND TROLLEYBUSES OF THE LONDON TRANSPORT EXECUTIVE

Conductors							Drivers						
Age of Men in 1949–1950 (Years)	Number of Men Observed	Incidence—First Clinical Episodes—of Coronary Heart Disease	Mortality Rates per 1,000		First 3 Years		Age of Men in 1949–1950 (Years)	Number of Men Observed	Incidence—First Clinical Episodes—of Coronary Heart Disease	Mortality Rates per 1,000		First 3 Years	
			First 3 Days (1)	First 3 Months (2)	No. of Deaths	Rate (3)				First 3 Days (1)	First 3 Months (2)	No. of Deaths	Rate (3)
35–39	2955	*0·0*	*0·0*	*0·0*	0	*0·0*	35–39	3179	*0·3*	*0·0*	*0·2*	1	*0·2*
40–44	1856	*0·0*	*0·0*	*0·0*	0	*0·0*	40–44	3002	*1·0*	*0·3*	*0·3*	2	*0·3*
45–49	1438	*1·7*	*0·4*	*0·4*	1	*0·4*	45–49	3213	*2·2*	*0·8*	*0·9*	8	*1·2*
50–54	1322	*2·3*	*0·8*	*1·1*	4	*1·5*	50–54	2636	*2·9*	*1·0*	*1·3*	10	*1·9*
55–59	1199	*5·0*	*0·4*	*0·8*	4	*1·7*	55–59	1892	*5·3*	*1·9*	*2·9*	12	*3·2*
60–64	813	*5·5*	*1·2*	*1·8*	4	*2·5*	60–64	1442	*7·6*	*2·1*	*3·8*	14	*4·9*
Standardized Rate at 35–64 Years		*2·0*	*0·4*	*0·6*		*0·8*	Standardized Rate at 35–64 Years		*2·7*	*0·9*	*1·3*		*1·6*

The incidence includes all first clinical episodes of coronary heart disease that were recognized and recorded in these men in 1949 and 1950.

The mortality rates are cumulative : (2) includes (1) and (3) includes (2). Since they result from the cases occurring in two years the denominators used are *twice* the "numbers of men observed". This conforms with the idea of an annual incidence, and shows the number of deaths which occurred (within the specified time) amongst the new cases arising in any one year amongst 1,000 men.

Mortality rates are standardized for age on the civilian male population of England and Wales in 1949.

Details of populations and methods of recording sickness absence and deaths are given in *The Lancet* (1953) **2**, 1053.

of mortality from four months to three years was 0·2 (conductors) and 0·3 (drivers) and this adds up to a total mortality in the three years of 0·8 and 1·6 respectively.

The advantage in the conductors' experience over the drivers' is thus apparent at 0 to three days, four days to three months, and four months to three years. But there is an indication that with the passage of time the advantage is becoming smaller. Eventually, it is reasonable to anticipate, the coronary mortality among these men will approximate to the incidence—2 per 1,000 in the conductors and 2.7 in the drivers—an overall superiority in the conductors of about 35%, compared with that of 125% in the "immediate mortality" reported above.

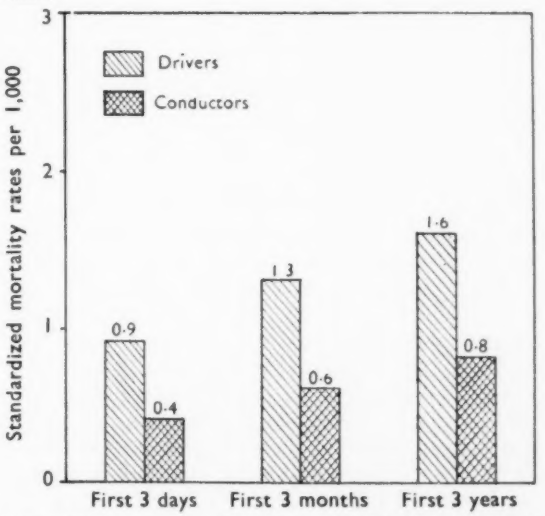
Forty per cent. of the conductors and 60% of the drivers who had a first attack in 1949 and 1950 died within three years. The Table gives details of the results and Fig. 1 summarizes them.

An Hypothesis

Nearly all the conductors' work is on double-decker vehicles. On the basis of the above observations, and others, an hypothesis has therefore been stated as a guide to future investigation :

> That men in physically active jobs have a lower incidence of coronary heart disease in middle age than men in physically inactive jobs. More important, the disease is not so severe in physically active workers, tending to present first in them as angina pectoris and other relatively benign forms, and to have a smaller early case fatality and a lower early mortality rate.

It should be emphasized that the hypothesis is not advanced in any exclusive sense—that differences in their physical activity at work is the only factor relevant to the differences in coronary disease described or, necessarily, the main one. But if progress is to be made questions must be narrowed down, and they are often best dealt with one at a time.



Cumulative mortality from onset of first clinical episode
First 3 days = "Immediate mortality"
First 3 months = "Early mortality"

FIG. 1.—Mortality from coronary heart disease in male drivers and conductors, 35 to 64 years of age, working on central buses, trams, and trolleybuses of the London Transport Executive.

So far, we have only been able to do little by way of testing the hypothesis in these transport workers. Following are the kinds of questions that arise :—

Is the Hypothesis True?—The difference between 2.0 and 2.7 in the incidence of the disease probably underestimates the real difference between the conductors and drivers. The excess of angina in the conductors may well be due simply to their physical activity evoking symptoms which in the less active drivers remained quiescent and undetected. That is to say, the figure of 2.0 in the conductors is very likely an inflated one relative to the 2·7 of the drivers.

We are, however, thinking of another possibility : that conductors, more than drivers, exclude themselves from conducting and weed themselves out of the population at risk, because of early or subclinical manifestations of coronary heart disease, such as fatigue or diminished exercise tolerance, which are brought on by physical effort. There is no evidence to support such a possibility, and it is not yet apparent how it may be investigated. If it were real it would of course be very important. (It should be remembered that men are unlikely to give up conducting for health reasons without reporting to the Medical Department, because of the efforts made to place such men in alternative employment, and because there may be an *ex gratia* benefit involved.)

If the Hypothesis is True, Is It Only Indirectly True?—This raises the big question of the other differences there are between conducting and driving, and the many differences there must be between conductors and drivers : *must be* because they have chosen such very different jobs. Are the mental strains of conducting less than those of driving? Do conductors have different kinds of constitution, or health histories, eat less, smoke less, have more active leisure pursuits? As a first approach to this kind of question, we have started an analysis of the size and shape of conductors and drivers, using their uniform measurements as an indicator. A first sample of about 1,000 men is promising : there are interesting similarities and differences in the measurements ; and, most interesting, these are as clear at 25 to 34 years of age, in the earliest years of conducting and driving, as at 55 to 64.

The alternative and better way to meet this possibility that in dealing with differences in physical activity of jobs we may, in fact, be dealing mainly with a partial correlation between physical activity and another factor, is to observe the operation of physical activity in a wide variety of situations so that eventually it becomes the only constant factor. This has been attempted elsewhere, and similar differences in respect of coronary disease were identified between postmen and sedentary workers ; and between " heavy " workers, generally, and " light " workers.

If the Hypothesis is True, How is Physical Activity Effective?—An observation relevant to this problem is the substantial difference in severity of the disease among the two groups. It is interesting first to compare the mortality experience in relation to the mode of clinical presentation :

Type of First Episode	Total No.	No. Dying		% Surviving 3 Years
		First 3 Months	4 Months–3 Years	
As angina pectoris	22	1	1	91
As " coronary thrombosis "/ myocardial infarction	89	46	12	35

This advantage to those who present with angina and (presumably) without major infarction was originally shown in the survey of medical practitioners. The present further evidence is strong, as it comes from a " prospective " study, the diagnoses having been made during the first episode in 1949–50 and not changed since then. Now it is known from general experience that many cases first coming to clinical notice with a major occlusion/infarction have previously had angina which was not particularly troublesome ; and, anyhow, had not led them to seek advice as a result of which the diagnosis was made. Conductors, of course, presented more commonly with angina than drivers. (Why this is so has already been briefly discussed : they would be less likely to ignore the pain.) The question therefore arises, Can it be that their detection of the disease at an earlier, or less serious, stage by the conductors and the subsequent adjustment of their way of living have helped to reduce their coronary mortality? It should be noticed that the fatality rate in the cases presenting as major occlusion/infarction was similar in the two groups ; the advantage of the conductors was that so many of their cases presented as angina. This question needs to be gone into in detail, and with much larger numbers than we have been able to study. It illustrates another kind of relation—between occupation and health—apart from the aetiological, with which we are mainly concerned at present.

However, it is unlikely that this mechanism can account for all the difference in mortality between

the two groups which has been observed. These are the numbers and distribution of first episodes in 1949–50 under 50 years of age :

	Total No. of First Episodes	Presenting as—		
		Angina Pectoris	"Coronary Thrombosis" with Early Mortality	Other "Coronary Thrombosis"
Conductors	5	1	1	3
Drivers ..	22	0	9	13

Clearly, there must be another factor in early middle age which produces the difference between the mortality of drivers and conductors. The cases of angina in the conductors which could have operated in the manner described in the preceding paragraph just did not occur.

If the Hypothesis is True, What are the Implications for Preventive Medicine?—The question arises at once of the amount and nature of physical activity outside work. Do conductors and drivers differ? More specifically, for example, have the drivers who do not develop coronary heart disease more active leisure interests than those who do?

Natural History

Several features of the natural history of coronary heart disease may be illustrated from the present material. For example, the curve of mortality in the clinical disease is a peculiar one, very much like that of infant mortality, the greatest danger being in the first days, and diminishing steeply thereafter. Fig. 2 shows that of the 60 coronary deaths in the three years of observation, 31 occurred in the first three days of the first clinical episode, a further 16 in the remainder of the first three months, and 13 in the next 33 months. This distribution is similar to the experience of the medical practitioners previously studied. However, the prognosis after the early weeks of the first clinical episode is not so good among these transport workers as among the doctors. This may be a reflexion of difference in social circumstances, or in treatment, and it should be investigated further.

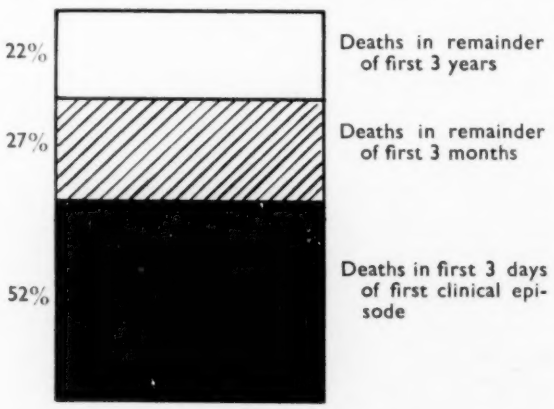

22%
27%
52%
Deaths in remainder of first 3 years
Deaths in remainder of first 3 months
Deaths in first 3 days of first clinical episode

FIG. 2.—Deaths from coronary heart disease in relation to first clinical episode.

Employment History

A brief analysis was made of the 50 men who were still alive at the end of three years. Sixteen (six conductors and 10 drivers) are still working in London Transport. Not one is in the job he held in 1949–50 : one man who had been a driver was now working as a conductor ; the other 15 were mostly employed as telephone operators, messengers, and queue pointsmen—jobs considered to be within their various physical capacities. The consensus of opinion in industrial medicine is that once a driver has demonstrated he has ischaemic heart disease, he can no longer be considered fit to drive passengers in a public service vehicle. In general, conducting is beyond the physical capacity of a man who has had an overt attack of coronary heart disease, though there are exceptions. Five of the 16 men still working with London Transport have already had further absences from work attributable to coronary heart disease. (Of course, others of the three-month survivors had been placed in alternative employment within the organization after recovery from their first clinical episode, and subsequently died or retired. Five conductors and six drivers come into this category, making 27 in all, of the 64 three-month survivors who had returned to work in the organization.)

Of the 34 (13 conductors and 21 drivers) who survived the first three months and were still alive when traced at three years, but not working with London Transport, 23 were under 65 years of age ; and of these 23, 13 were known to be in some form of employment.

In brief, therefore, there were 43 three-year survivors who were under 65 years of age and 29 of these are known to be working, 16 with the Executive and 13 elsewhere. At a later stage we may be able to make some report on the employment experience of those who left the Executive.

Comment

Two points may be made. Of the 111 men first presenting with coronary heart disease in 1949 and 1950, about 45% survived for three years or more. Many of these are in active employment as described

above. There is urgent need for more systematic study of the needs and capacities of the tens of thousands of men who have " had a coronary " and subsequently returned to work. Careful follow-up studies are required of these men over the years, comparing their experience under different medical and occupational régimes. Finally, it may be noted that this type of enquiry deals with a general relationship between work and health, in contrast to the specific occupational hazards with which industrial medicine has been obliged to be so much concerned in the past. The industrial medical officer working in the field is well placed to study such questions ; and occupational medicine may have a great contribution to make in this way towards the elucidation of major problems of the aetiology and natural history of disease, and of the rehabilitation of the sick, by using its every-day opportunities for the observation of men at work.

We are very grateful to our colleagues in the Social Medicine Research Unit, particularly Mr. J. A. Heady, and in London Transport Executive, particularly Dr. L. G. Norman, Mr. F. H. Spratling, and Mr. F. J. Lloyd, for much help.

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Brit. J. industr. Med., 1954, **11**, 265.

BURSITIS OF THE SHOULDER IN COAL MINERS USING BORING MACHINES

BY

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(RECEIVED FOR PUBLICATION MAY 18, 1954)

The boring machine may in certain circumstances cause well-defined lesions of the skin and deeper structures of the shoulder loosely termed " beat shoulder ". Although these lesions have not been specifically described many doctors in mining areas are aware of their association. We have examined clinically 35 full-time borers only three of whom presented themselves for treatment at a colliery medical centre. The rest were selected at random from six collieries which gave a wide range of work in different thicknesses of seam, a factor which was early realized to be important.

The Machine and Working Environment

The boring machine with trailing cable weighs approximately 40 lb. It is not a percussive tool but consists of a long drill driven by an electric motor having a substantial base against which the men push (Fig. 1). The electric motor is geared down from 2,400 r.p.m. to 750–500 r.p.m. on the actual drill.

At intervals along the coal face holes are bored to depths varying from 2 ft. to 4 ft. 6 in., that is 6 in. less than the depth of coal cut by the coal-cutting machine. When the coal is cut near the floor the holes are bored near the roof or, alternatively, near the floor when the coal is cut near the roof. The former is more common. Explosive is inserted into the hole and then fired to loosen the coal. A full-time borer will bore between 70 and 150 holes per shift of seven and a half hours. For top hole boring the borer presses his shoulder against the base of the boring machine, the relationship of this base to the shoulder region varying with seam thickness and the idiosyncrasy of the operator. For bottom hole boring the borer usually uses his feet.

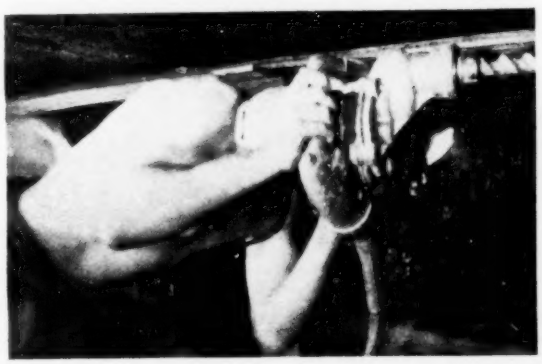

FIG. 1.—The boring machine.

When roadways are enlarged or developed boring occasionally is required, and here it is in stone, not coal.

The majority of cases we have described are of borers drilling in coal.

Clinical Findings

The exact relationship of the skin of the shoulder to the base plate of the machine plays a large part in determining the variance in the clinical picture, this in turn being related to the seam thickness and personal habits of the operator. The tissue changes in the region of the shoulder are in the skin (bruising, pigmentation, and sepsis) and in the formation of bursae, of which two types are described ; one lying near the point of the shoulder being superficial and subcutaneous, the other lying medially below the lateral third of the clavicle and partially deep to the medial fibres of deltoid. This latter bursa may be a continuation of the sub-deltoid bursa. Three cases were radiographed (one in Group II and two in Group III) and showed no abnormality.

Cases Grouped According to Physical Signs

The borers could be divided into four groups.

Group I.—Nine men had no signs or symptoms.

Group II.—Eight men each had a large bursa situated below the lateral third of the clavicle, also showing diffuse skin changes.

Group III.—Ten men each of whom had a bursa in the shoulder tip region, being subcutaneous and superficial to the acromial process but usually below it. The skin changes here were more localized than in Group II.

Group IV.—In this group of eight men there is a painful shoulder but no swollen bursa or skin changes.

Clinical Features of Each Group

The table is a summary of the chief features of each group.

Group I.—These men had neither subjective complaints nor any abnormality on physical examination. The average age of the group was 36 years and all worked in seam thicknesses of 4 ft. 6 in. and above, and in a seam of this thickness, although the shoulder is used, it is possible for a fellow workman to lend support to the base of the machine by standing behind the operator and pushing forward with his hands. The general feelings of the men supported this view. The average number of years spent boring was 3·7.

Group II.—The deltoid muscle takes its origin partly from the outer third of the calvicle, and in the eight cases seen in this group a bursa was emerging from the lower border of these clavicular fibres. The bursa was large and could have been an enlargement of the sub-acromial bursa (Fig. 2).

Skin changes were largely bruising and pigmentation, and we were informed that the bruising was most prominent at the week-ends when the men were resting from work. The skin changes were very

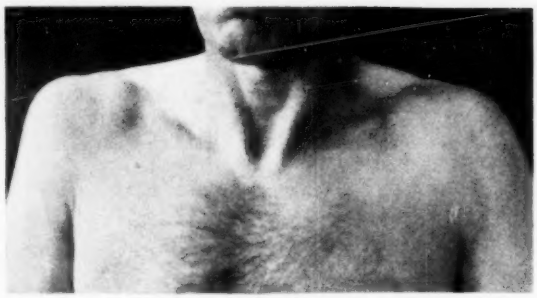

FIG. 2.—A bursa lying below the lateral third of the right clavicle.

diffuse and extended over the anterior aspect of the shoulder into the infra-clavicular region. Scratch marks in the region of the spine of the scapula, due to the apposition of the back to the roof during boring, were very well marked. These may become infected and so contribute to the inflammation of the bursa.

A typical history in this group was one attack of pain in the shoulder followed by swelling. We were fortunate to see two of these cases from the onset and to follow them up. During the acute, painful phase, which lasted only two to three days, in one case there was marked limitation of all shoulder movement, and in the other specifically painful abduction through the range 60° to 120° and on external rotation. Both these patients complained of a cold hand on the same side as the shoulder lesion, and on examination the hand was certainly cold. The swollen bursae persisted for three months and six months, but the men were back at work after an absence of only two and three weeks.

The other six cases were seen in the chronic state

TABLE
CLINICAL SUMMARY OF GROUPS STUDIED

Group	No. of Men	Average Age (years)	Years Boring	Seam Thickness (ft. in.)	Type of Pain	Skin	Bursa	Joint Movement	No. of Hand Symptoms	Average Time Lost per Attack
I	9	36	3·7	4 6 and over	—	—	—	—	—	—
II	8	40	12	3 0 (one case 4 0)	Single acute, short attack	Diffuse bruising, pigmentation of varying degree	Deep subdeltoid	Affected during acute stage only	4	Days only
III	10	34	7	3 6 (2 cases 4 6)	Slight, worse at work	Marked localized pigmentation, sepsis in 3 cases	Superficial	—	5	Days only
IV	3	59	26	Greater than 4 6	Continuous, severe, better at work	—	—	Marked fixity	3	Weeks
IV	5	49	7·5	4 6 (2 cases 3 0)	One severe attack	—	—	Affected during attack	3	Weeks
Total	35	48	9	—	—	—	—	—	15	—

during which there is slight shoulder pain, insufficient to keep them off work, together with the swollen bursa, but no limitation of shoulder movement. The pain was sometimes worse in bed at night.

The average age of the men in this group was 40 years. Each man bored approximately 75 holes per shift, using his shoulder, and had spent 12 years boring. The seam thickness was 3 ft. in all cases except one (4 ft.) and in two cases the trouble arose immediately on transferring from a thicker seam to a seam 3 ft. in thickness. The other cases blamed poor quality of the bits which are fitted on to the end of the drill, or a particularly hard piece of coal.

Two cases in the group and one of the third group showed a localized patch of growing hair about the size of a five-shilling piece which, we were told, grew long and silky during their holidays. The significance of this is difficult to assess, but we felt that it was in some way related to the friction occasioned by the base of the boring machine.

Group III.—There were 10 men in this group, eight of whom came from one pit. The distinguishing features were well-marked skin changes and a well-defined subcutaneous bursa situated over the greater tuberosity of the humerus and the bicipital groove in the region of the shoulder tip. The bursa is well demonstrated in Fig. 3, being lateral and more

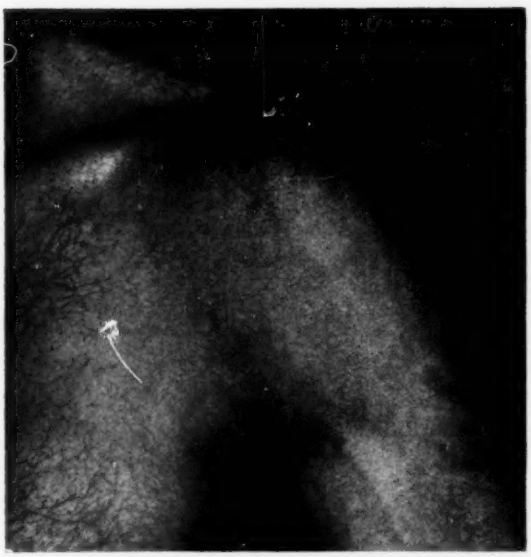

FIG. 3.—Subcutaneous bursa of the left shoulder, showing the coal particles embedded in the skin over the bursa.

superficial than the bursa in Group II. Fig. 4 shows superficial and deep bursae together in the same person. The superficial bursa on the shoulder tip has been partially aspirated and had no connexion with the deep bursa.

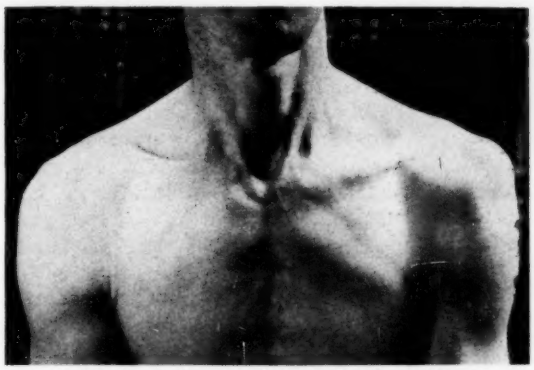

FIG. 4.—Both types of bursa in the left shoulder.

Sepsis is frequent in the group and the skin changes are well marked (Fig. 5).

It is suggested that this is an adventitious bursa which develops as a result of the frictional pressure of the " ram's head " (base of the boring machine). The history of these patients differs from those in

FIG. 5.—Skin sepsis over superficial bursa.

Group II. Three men complained only of slight soreness and two had slight pain only when boring, which passed off an hour or so after the shift. Two had intermittent attacks of pain occurring at monthly intervals, lasting a day or two, during their first two years of boring, but had no trouble since. Two others were still in the intermittent painful stage, and one man aged 54 years had developed continuous pain only during the past 12 months after boring for 14 years without symptoms. This latter type of pain is much more common in Group IV.

The average age of this group was 34 years, *i.e.*, appreciably younger than Group II, and each man bored 80 holes per shift with his shoulder. Eight also bored a further 75 holes per shift using their feet

(they work on a contract basis). This is mentioned because boring at this speed requires greater pressure, and friction is likely to be more intense. Each man has been boring on the average seven years. The seam thickness was 3 ft. 6 in. in eight of the cases, and 4 ft. 6 in. in two other cases.

Another notable feature was that eight men used their left shoulder, although they were all right-handed. The reason for this was that if the drill struck a particularly hard piece of coal the machine was thrown to the left and could do least damage to the face.

Group IV.—This is a miscellaneous group of eight men, in none of whom was there any skin or bursa changes on examination, but all complained of a painful shoulder. Three of them had had continuous pain in the shoulder for two, four, and five years. The pain was severe and extended down to the insertion of the deltoid and up to the trapezius muscle in the neck. The pain was better after an hour at work and most severe in bed at night. One man actually sleeps in a chair because he is unable to lie on the affected shoulder. In these three cases abduction and external rotation were severely limited and it is probable that they were cases of periarthritis or pericapsulitis of the shoulder.

The average age of these three men was 59 years, and each bored approximately 67 holes per shift. Together they had bored for 79 years. The pain in these cases was more severe than in the other groups and more time was lost.

The fourth case was seen during his first attack of pain after boring for seven years in rock and stone. The attack lasted three weeks and was a typical supraspinatus lesion. He worked in seams of greater thickness than 4 ft. 6 in. and had lost two weeks' work. Three other men had had similar attacks of pain, being unable to play darts or remove their shirts.

The average age of this group was 53 years, and it is doubtful if their symptoms can be specifically related to boring, as this type of lesion is so common in older people irrespective of their occupation (Nicoll, personal communication). It is possible, however, that boring may make the condition worse.

The last patient in this group is worthy of separate comment. He was aged 48 years and had been boring for seven years but had given up this work 18 months before because of a painful shoulder. The pain began from the first day of working, building up to a crisis approximately every month. Altogether he lost 252 working days in a period of seven years. The pain radiated down the radial border of the forearm, and, according to the patient, he lost his power of grip. Tingling and numbness appeared in the thumb and first two fingers of the hand from the first day of boring and increased in intensity coinciding with the crisis of shoulder pain. There were no physical signs when we examined him, but it is possible that this syndrome may have been occasioned by a functional abnormality of the thoracic outlet as in the two men in Group II who had a cold hand on the affected side.

Hand Symptoms

Those borers with no signs or symptoms referable to the shoulder made no complaint of their hands. Of the other 27 cases, 15 had subjective hand symptoms. Three of these men have already been mentioned and one other case had one spell of tingling and numbness of his right hand, which coincided with the attack of shoulder pain. Of the other 11 cases, deadness and numbness of the hands was a more frequent complaint than pain or tingling. In four cases it was bilateral and the following phrases are most expressive: "I suck them to life every morning upon getting out of bed." "I have to slap my hands on the side of the bed to restore them to life." "I often sleep with my hand hanging over the edge of the bed in order to keep it alive."

Apart from occurring in bed, these attacks were precipitated by reading the paper with the hand elevated and during and directly after a shift. In the other seven cases the symptoms were confined to the hand on the side of the shoulder which was used for boring, and there were no symptoms in the other hand. The middle and ring fingers were most commonly affected.

These symptoms are presented in order to complete the picture of the hazards of the boring machine. The incidence of approximately 43% is sufficiently high to suggest that they are of occupational origin, but no explanation of their exact nature or the mechanism by which they are produced can be made from the results of our examination, which was not sufficiently comprehensive nor specifically directed with this object in view.

Summary

Thirty-five full-time borers have been examined and the results of the clinical findings are detailed.

A new adventitious bursa is described and was found in borers working mainly in seam thicknesses of 4 ft. and below.

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A SOCIAL AND OCCUPATIONAL STUDY OF THE CAUSES, COST, AND PREVENTION OF INFECTIONS OF THE HAND

BY

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Although there are many books and papers dealing with the treatment of hand infections and also with the bacteriology of wound infection and sepsis, little has been published about the social and occupational aspects of hand infections.

In this study the following questions were considered: What is the cost of a hand infection, measured in terms of money and working time lost by the patient? What part do social and occupational factors play in the origin and development of sepsis? How can infections of the hand be prevented?

Method

The patients concerned in this enquiry were all attending the hand clinic of the department of surgery in the Royal Victoria Infirmary, Newcastle-upon-Tyne. All casualties are first reported to the accident room of the hospital where minor lacerations are dealt with, but all serious hand injuries or infections are referred to the hand clinic. Dormitory accommodation is provided in a hostel attached to the clinic, and almost all the adult patients are admitted to the hostel, where, on the average, they stay for three days for infections and seven days for injuries.

The research included injuries as well as infections of the hand, but this report is concerned only with hand infections, and data compiled from the injuries research are not mentioned except for purposes of comparison. When comparisons are made the groups will be distinguished by referring to the injuries as the "trauma group" and the infections as the "sepsis group".

The patients were all men of working age, and they were interviewed in the hostel during 27 of the weeks in the period beginning March, 1952, and ending mid-December, 1952. The total number of patients with infected hands (and fingers) interviewed during that period was 151. Of these, 106 (70%) gave a definite history of injury (sepsis following injury), while 45 (30%) could not remember an injury to the hand before the onset of infection (sepsis but no known trauma). In the interests of accuracy, patients were asked to state when and how the injury occurred, with relevant dates, and patients who could not remember an injury but thought that they must have injured the hand were classified with the patients giving no history of injury. Patients were not selected; all the new patients who were in the hostel during the weeks of interview were seen.

Direct questioning was avoided as far as possible. Once the factual information relating to dates, times, and incomes had been obtained, the interview became a discussion on how the patient's particular hand infection had occurred, and also on the general problem of industrial sepsis. The information was recorded on a schedule which had been designed to cover the main points of the enquiry.

Limitations of Method.—One of the most important limitations of the method concerned the difficulty people have in remembering the details of any event in their lives occurring more than a week or two before. Care was taken to guard against errors from this source, and in cases of obvious confusion patients were asked to trace the history of their illness with the aid of a diary. Fortunately, histories did not often go far back, and there is no reason to suppose that most of the dates given were not accurate, but where there was doubt about the dates given they were classified as date unknown.

Again, much of the interesting and valuable information consisted of patients' opinions—as, for example, that on first-aid facilities and the use of safety gloves—and could not be described numeri-

cally. The data here are necessarily nebulous, but not valueless on that account. In general, the study was made from the point of view of the patient, and there is no evidence to suggest that patients have evaded the issue or not given an honest opinion. It is possible that some patients tended to underestimate the interval from injury or onset of infection to first treatment; but this is regarded as unlikely, partly because exact dates were always asked for, and partly because it is reasonable to suppose that after one or two sleepless nights caused by the discomfort of an infected hand the patient would seek treatment as soon as possible.

Results

The Diagnoses.—Most of the patients who attend the clinic have well-established infections, and all those who were interviewed had infections severe enough for them to stay for a few days in the hostel. The diagnoses of the patients are set out in Table 1.

TABLE 1
MEDICAL CLASSIFICATION OF THE INFECTIONS

Type of Infection	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
Infection around nail	14	13	10	22	24	16
Infection of pulp space	19	18	10	22	29	19
Subcuticular	1	1	3	7	4	3
Subcutaneous	52	49	13	29	65	43
Carbuncle	—	—	1	2	1	1
Tendon sheath infection	1	1	1	2	2	1
Deep palmar spaces	8	8	3	7	11	7
Cellulitis	2	2	1	2	3	2
Miscellaneous	9	8	3	7	12	8
Total	106	100	45	100	151	100

In both the traumatic and non-traumatic groups most of the infections were subcutaneous, infections of the pulp space, and infections around the nail.

Nearly all the patients had had treatment of some kind before attending the clinic, the majority being sent up by their doctors. Occasionally a patient came up on his own initiative, but this was unusual. The remainder of the patients were sent to the clinic by other hospitals or by industrial first-aid departments.

The Occupations of the Patients.—To what extent are infections of the hand related to occupation? If infection is attributed to injury, how was the injury caused and is it a hazard of some particular occupation? If the infection has no history of injury, is it nevertheless related to some type of employment?

Not all the injuries occurred at work, and Table 2 includes 18 patients (17%) in the sepsis group who were injured away from work, usually at home. For purposes of comparison Table 2 also includes figures relating to the trauma group of patients. Unfortunately the figures, especially for the group with sepsis unrelated to injury, are extremely small, but one or two points are worth making. An interesting point, also noted by Robins (1952), is that mining accounted for a far higher proportion of the injuries than of the infections. Forty per cent. of the patients in the trauma group were miners compared with only 19% of the patients with infected hands. Of the 29 miners with infected hands, nearly a quarter (seven patients) were datal (day rate) workers, and the rest worked in a variety of jobs, mostly at the coal face.

TABLE 2
OCCUPATIONS OF THE PATIENTS

Occupations	Number of Patients							
	Sepsis						Trauma Total	
	Traumatic		Non-traumatic		Total			
	No.	%	No.	%	No	%	No.	%
Mining	25	23	4	9	29	19	119	40
Engineering	21	20	9	20	30	20	70	23
Woodworking	4	4	1	2	5	3	30	10
Unskilled	7	7	3	7	10	7	23	8
Transport	11	10	2	4	13	8	6	2
Building and contracting	7	7	3	7	10	7	8	3
Others	31	29	23	51	54	36	41	14
Total	106	100	45	100	151	100	297	100

The other large occupational group was engineering, and this was expected, partly because nearly a quarter of the adult males on Tyneside work in the engineering industries, and partly because men working in these industries are exposed to the kind of trivial injury which, it is known, often leads to infection. The Registrar-General's Classification of Occupations, 1950 (General Register Office, 1951), has been used throughout this study, and in this classification engineering and allied trades covers a large number of different trades, including some shipyard workers (but not labourers). No one group within engineering was noticeably larger than any of the others, but the men were all doing jobs where they might easily knock, cut, or blister their hands, or where there was danger of injury from metal filings. Unskilled workers, and workers in transport and communication, and in building and contracting, made up between them 22% of the total.

Data from the trauma group have been included in the last column of Table 2, so that a comparison can be made between the two groups of patients, and it will be seen that there is a striking difference in the distribution of occupations between the two groups.

Only 14% of the total number of patients in the trauma group were in occupations listed under " Others " (11 different occupations), whereas the patients in the sepsis group mentioned so great a variety of jobs that the classification " Others " includes 16 different occupations and comprises 36% of the total. Seven was the largest number of patients included in any one of these occupations, but usually there were no more than three or four patients in each group, and sometimes only one. The most frequently mentioned occupations were personal service (chefs, chimney sweeps, etc.), agriculture, clerical work, metal manufacture, makers of food or drink, and printing. Six of the men were unemployed.

How the Injury was Caused.—Table 3 very clearly brings out the smallness of the injury which led to the infection. This Table includes only the injuries occurring at work, and it is interesting to find that 65% of the total number of these injuries occurred as a result of knocking the hand against something, usually a piece of rough metal or a splinter of wood, wire, or glass. A number of patients sustained tearing, cutting, or pinching injuries when the hand was hit by something falling on to it. Usually this type of accident occurred when goods were being handled, but three of the patients had hit themselves with a hammer. The other large category of injuries consisted of blisters. These most frequently occurred when the hand was rubbed against a tool handle for a considerable period of time. A blister resulted either when the tool handle was rough, or when, for some reason, the skin on the hand was soft. Amongst the injuries classified under " Other " were two burns.

TABLE 3

CAUSE OF THE INJURY

Injury Caused by	Number of Patients									
	Piece of Metal		Hand Tools		Splinters		Other		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Knocking against	24	96	4	21	19	100	10	40	57	65
Hit by	1	4	3	16	—	—	9	36	13	15
Rubbing against	—	—	11	58	—	—	1	4	12	13
Other	—	—	1	5	—	—	5	20	6	7
Total ..	25	100	19	100	19	100	25	100	88	100

Eighteen of the patients were injured away from work, mostly at home or in the garden. Ten of these men were in white-collar jobs. Wood splinters were responsible for five of the injuries, and five of the men blistered their hands while rowing, playing golf, or digging in the garden. The blisters all occurred in clerks and others not normally engaged in heavy manual labour, and this serves to illustrate the point, often made by the patients, that hands blister easily if strenuous manual work is undertaken when the skin on the hand is not hardened to rough work. This happened to labourers returning to their jobs after a holiday or a bout of illness, as well as to professional or clerical workers doing some unaccustomed manual labour.

Intervals

From Injury to First Treatment.—A point which is often stressed when prevention of infection is being considered is that workpeople should report to the first-aid room for every injury, no matter how trivial, since it is thought by some that immediate treatment of all injuries would considerably reduce the sepsis rate. It is therefore interesting to note that a high proportion of the patients with infected injuries did in fact report injury and receive treatment immediately after the accident. Out of a total of 106 patients with a known history of injury, 21 (20%) received treatment straight away. The wound later became septic either during treatment (17 patients), or else the wound was treated once and was thought to need no further medical attention, but later symptoms of sepsis developed and the patient had to report again. Four more of the patients reported for treatment on the day of the injury, but as these patients waited for several hours before reporting, they have not been included in the above figures. Approximately half of the patients (55) reported for treatment within three days of the injury, and of the remaining 51 patients, 40 received treatment within two weeks of the injury.

From Onset of Symptoms to First Treatment.—Table 4 shows the interval between the time when the hand first started to trouble the patient and his first treatment after he noticed the symptoms. Some of the patients with infected injuries developed symptoms while the injury was receiving treatment, and these patients have been classified under the heading " Being Treated ".

It is clear from Table 4 that a large majority of the patients (76%) reported for treatment either before the development of symptoms or within three days of the onset. The two groups of sepsis patients differ slightly in that there is a tendency for the non-traumatic group of patients to report for treatment rather later than the others. This was not surprising since to the patient there would seem to be a greater chance of an infection clearing up by itself if it just came by itself without any injury to cause it. In the " Not Known " group were included patients who

TABLE 4
NUMBER OF DAYS BETWEEN ONSET OF SYMPTOMS AND FIRST TREATMENT AFTER ONSET

Number of Days	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
Being treated ..	19	18	—	—	19	13
No delay ..	20	19	6	13	26	17
1–3	48	45	21	47	69	46
4–9	7	7	13	29	20	13
10 and over ..	—	—	3	7	3	2
Not known ..	12	11	2	4	14	9
Total ..	106	100	45	100	151	100

either did not know the date of first treatment, or could not remember when the hand first started troubling.

From First Treatment to First Attendance at the Clinic.—Most of the patients had been receiving treatment from their general practitioner before attending the clinic, and on the whole they came to the clinic fairly soon after first reporting for treatment. Table 5 shows that over half the patients

TABLE 5
NUMBER OF DAYS BETWEEN FIRST TREATMENT AND FIRST ATTENDANCE AT THE CLINIC

Number of Days	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
No delay ..	16	15	14	31	30	20
1–3	47	44	13	29	60	40
4–9	30	28	11	24	41	27
10 or more ..	13	13	7	16	20	13
Total ..	106	100	45	100	151	100

(60%) were treated for three days or less before attending the clinic. Thirty of the patients (20%) did not delay at all, but came straight up to the clinic immediately after reporting for treatment to their doctor or works first-aid room. Other patients were treated for periods ranging from about a week to a month or more before they came to the clinic.

A higher proportion of patients with no known history of injury attended the hospital without delay than did the others, but since these patients tended to wait longer before seeking treatment in the first place (Table 4), it is possible that by the time the patient reported to his doctor the infection was very severe. Table 6 bears this out since it suggests that, on the whole, the infection was longer established in the group of patients with no history of injury than in the traumatic group.

TABLE 6
DURATION OF SYMPTOMS BEFORE ATTENDANCE AT THE CLINIC

Number of Days before Attendance	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
0–2	19	25	9	20	28	23
3–4	37	47	8	19	45	37
5–6	15	19	9	20	24	20
7–8	4	5	9	20	13	10
9 or more	3	4	9	20	12	10
Total	78	100	44	99	122	100

Duration of Symptoms before Attendance at the Clinic.—Twenty-nine of the patients could not remember how long they had had their symptoms before attending the hospital, and Table 6 shows the duration of symptoms for the 122 patients for whom this information is available. Of the total number of patients, rather more than half (60%) attended within four days of the onset of symptoms, but there was a difference between the two groups of patients. Over two-thirds (72%) of the patients with a history of injury attended the hospital within four days of the onset of symptoms, whereas only just over a third (39%) of the patients with no history of injury did so.

The Cost of the Infection

Length of Time Off Work.—From the economic point of view it is important to know how long the patient was off work, and whether he returned to his former employment. All the patients who were interviewed were given a form and asked to return it when they started work again, giving the date when they returned to work and stating if they had returned to the same or to a different job. This information was given by all but 13 of the patients. In addition, for various reasons, six of the patients were not working at the time of the enquiry. Information concerning the length of time the patients were off work was therefore available for 132 of the patients, and the data are set out in Table 7.

It is clear that the usual amount of time lost from work by patients in both groups was from two to four weeks, and 94 of the patients (72%) were back at work within a month. A further 30 patients (22%) were off for periods up to two months, and the remaining eight patients were off work for two to three months, the longest period of incapacity being 16 weeks (two patients). It was not possible to make an accurate estimate of working time lost in days, because some of the patients could only state approxi-

TABLE 7
NUMBER OF WEEKS OFF WORK

Weeks Off Work*	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
1	8	9	5	12	13	10
2	27	29	11	28	38	29
3	18	19	6	15	24	18
4	15	16	4	10	19	15
5	7	8	5	13	12	9
6	4	4	3	8	7	5
7	5	5	3	8	8	6
8	2	2	1	3	3	2
9 or more	7	8	1	3	8	6
Total	93	100	39	100	132	100

* Fractions of a complete week are reckoned as a complete week.

mately how long they were off work, but a rough average was about 24 days. If the eight patients who were off work for eight weeks or more are omitted from the calculations, the average time lost is reduced to 20 days.

Residual Disability.—It was not possible to obtain much information concerning residual disability, but it is known that seven of the patients returned to different jobs. This change did not always have anything to do with the hand infection. One boy was called up into the Army, another boy took up the apprenticeship he had been waiting for, and another patient, a miner, changed from datal (day rate) work to piece work, as the opportunity to do so presented itself at that time. One of the men reported that he had been on light work for two weeks while his hand hardened and then returned to his old job. Two of the men, a builder's labourer and a coal hewer, reported that although they had returned to their old jobs, after a week or so at work the hand was still tender and sore at times. One patient, a datal worker in the pits, was off work for three to four months with a subcutaneous infection of the right palm, and found that he could not do his job—putting up timber and general repair work—when he returned to the pit. He was then given a slightly lighter job, at a little less money, but that, too, was difficult for him, and when he was visited nearly a year after his injury he said he had lost a lot of time from work because of his hand. He was at that time off work because of another injury to his hand, and he said that he wanted work either on the surface or in a factory because there was a shortage of suitable light jobs down his pit.

A very large majority of the patients returned to their old jobs, and several of them wrote to say that the hand had healed well and had given no more trouble.

Financial Cost.—A rough idea of the alteration to the patients' incomes because of their incapacity can be seen from Table 8. It has only been possible to make a rough estimate of any alteration in the patient's financial circumstances, and the data take into account no more than the difference between the patient's average earnings at the time when he stopped work, and his personal income from Sickness Benefit, Injury Benefit, or other insurance benefits while he was off work. No note was taken of expenditure or the earnings of his family or any refund of Income Tax, because these were considered to be personal matters which the patient should not be expected to divulge.

The amounts lost each week by the patients varied enormously, and for the most part the losses ranged from £1 to £7 a week. This partly reflects the disparity between the wage rates in different occupations and age groups, and partly the different insurance payments paid to patients drawing Sickness Benefit and patients drawing Injury Benefit. Also, some patients had more dependants than others and therefore drew more in insurance allowances. Some of the patients drew allowances from their trade union or works sick or accident fund, and in some cases wages were made up by the employer, although the man might still stand to lose his overtime or bonus. The general picture given by Table 8 is

TABLE 8
DIFFERENCE BETWEEN USUAL EARNINGS AND INCOME DURING ILLNESS

Weekly Loss	Number of Patients					
	Traumatic Sepsis		Non-traumatic Sepsis		Total	
	No.	%	No.	%	No.	%
No change ..	12	11	13	29	25	16
Less than £1 ..	4	4	1	2	5	3
£1–£1 19 0 ..	13	12	6	13	19	13
£2–£2 19 0 ..	14	13	5	11	19	13
£3–£3 19 0 ..	14	13	4	9	18	12
£4–£4 19 0 ..	10	10	9	20	19	13
£5–£5 19 0 ..	13	12	1	2	14	9
£6–£6 19 0 ..	12	11	3	7	15	10
£7–£7 19 0 ..	5	5	1	2	6	4
£8 and over ..	8	8	2	5	10	6
Other	1	1	—	—	1	1
Total.. ..	106	100	45	100	151	100

that the loss varied around a mid-point of about £3 10s. a week, with a few patients losing £1 or less at one extreme and over £8 at the other. Twenty-five patients reported no alteration in income while they were off work, and this group included the unemployed, the retired, students, members of the Armed Forces, and those whose salary or wage was made up without loss. One man, classified under

" Other " did in fact lose heavily, but it was impossible to estimate the loss on a weekly basis. This man had a smallholding where he grew potatoes and cabbages, and there was no one to do the work for him while he was attending the clinic. His work was seasonal and while he might take £10 to £12 a week for six months or so, there were always times when his earned income was nil. Unfortunately the infection, acute paronychia of the left thumb, developed at the worst time for him, which was the middle of June when he was just about to plant out his summer and winter cabbages. He was off work for about a month because he could not hold anything in his hand. This made him a month late in doing his planting, and, to add to his troubles, September came in frosty with the result that he " may as well never bothered putting any out ". The cost to this patient could not be estimated exactly, but he wrote at the end of November to say that he thought he would have lost at least £150.

Social and Occupational Factors Concerned in the Development of Sepsis

It was clear both from the statements made by the patients and also from observation of the state of their hands that their hands had often received small cuts and trivial puncture wounds, but according to the patients the majority of these wounds did not become septic. The question is, Why do some wounds become septic when others do not? Also, are there any social factors which might cause infection to develop when there has been no apparent injury?

Some of the factors which may affect the development of sepsis, such as the condition of the hand at the time of injury, and the type of treatment received, are of concern to the surgeon, and they are not considered here. The emphasis here has been placed on the social and occupational factors only.

It was not possible to make an exact quantitative assessment of these factors, and the evidence is based on the statements made by the patients in the course of discussions on their particular hand infections, and also on the problem of industrial sepsis in general. Although the results in this section are qualitative, no conclusions are based on isolated instances or on very small numbers.

General Health of the Patients.—The patient's state of health at the time of the onset of sepsis is an important factor to consider. The patients were asked if they had had any illnesses during the previous three months or so sufficiently severe to keep them away from work, and also whether they thought the onset of infection had anything to do with their general health. The trauma group of patients were also asked about their general health, with the explanation that the question was asked because of the possible relationship between the health of the worker and his susceptibility to accidents. It was made clear to all the patients that the purpose of this question was to find a possible cause of their accident or infection, and that it did not refer to their feelings after the injury had happened or sepsis had developed. It was thought worthwhile to compare the findings of the two groups, and these have been analysed in Table 9. No great exactness is claimed for this Table, chiefly because it is possible that the patients in the sepsis group may have been more ready with their answers because they had, perhaps, already considered the question.

TABLE 9
STATE OF HEALTH OF THE PATIENTS

State of Health before Present Illness	Number of Patients							
	Sepsis						Trauma Total	
	Traumatic		Non-traumatic		Total			
	No.	%	No.	%	No.	%	No.	%
Recent illness* ..	3	3	5	11	8	5	25	8
Run down ..	26	24	13	29	39	26	8	3
Fit and no illness	77	73	27	60	104	69	264	89
Total ..	106	100	45	100	151	100	297	100

* " Recent illness " means any illness during approximately three months before the interview and which caused the patient to lose time from work.

It will be seen from this Table that nearly a third of the sepsis group of patients (31%) had some illness or " run down " condition to report, whereas the trauma group of patients had a much cleaner bill of health; all but 11% of the trauma group of patients felt fit at the time of injury and had been clear of incapacitating illness for at least three months before the interview. Another noticeable difference between the two groups of patients was that there were more " run down " conditions in the sepsis group than in the trauma group. Of the total number of patients with infections, over a quarter (26%) complained of a feeling of unfitness at the time of the onset of sepsis, but only 3% of the trauma group of patients said that they were not feeling fit at the time of the injury.

The term " run down " is a vague one, and when the patients mentioned it they were asked if they had any symptoms in support of this feeling. The most frequently mentioned trouble was boils, and several of the patients mentioned constant sore throats and an inability to throw off colds. Others had no physical symptoms but said that they always felt tired and did not feel like doing anything much after working hours. Two of the men were attending

their doctors because they felt in need of a tonic, and one man had just taken a week off work because he did not feel well. A few of the patients were unmarried and living in lodgings, and some of these patients complained of inadequate food and loss of weight.

The illnesses mentioned by the patients were too varied to classify, but the most frequently mentioned complaints were stomach troubles and chest troubles.

Twenty-four of the sepsis group of patients had had septic conditions of some kind, usually to the hand, within the previous two years. Although this may be a reflexion of the job rather than of the man, it is not too fanciful to suppose that some people are more prone to sepsis than others. As one patient remarked, "With me every scratch turns septic."

Reasons for Delay in Seeking First Treatment

Neglect.—On the whole the patients did not wait an unreasonable amount of time before seeking treatment. Forty-five of the patients (30%) reported for first treatment either immediately after the injury or as soon as the hand started to trouble them. For these patients the question of neglect does not arise, unless it is always considered neglectful to wait for an injury to become infected before reporting it. The remaining 106 patients waited for at least one day after the onset of symptoms before seeking treatment. The reason given for the delay was usually that when the hand started to trouble them it did not seem to be worth bothering about, and the patients hoped that if they treated the hand themselves the infection would clear up. It was only when the hand became really painful that these patients considered a visit to the doctor to be justified. This attitude is easy to criticize until it is remembered that for the patient a visit to the doctor can be a tedious and time-consuming business. There was the feeling, too, that the doctor might not give a favourable reception to a patient who took up his time with a trivial complaint like a sore finger. A few of the patients had obviously gone on hoping for the best for too long after they might reasonably have been expected to seek expert attention, but in no case did a patient put up with a painful or throbbing hand for more than two or three days. Such delay as there was occurred when the hand was merely sore or red looking. Usually when a patient had waited more than four or five days before seeking treatment it was either because the infection seemed to have cleared up but had broken out again, or else the infection had been slow in developing. Treatment given at home was mostly bathing or poulticing, but a few of the patients squeezed the wound to bring it to a head, or explored it with a needle or a pin in search of a foreign body.

The Week-end.—A suggestion is made by the Chief Factory Inspector in his Annual Report for 1950 that the week-end plays a part in the development of sepsis. The evidence here supports this suggestion. Twenty-six of the patients said that they would have gone to their doctor earlier had it not been for the week-end. This happened when the injury occurred or the sepsis developed on Friday or Saturday, but the patient did not attend for treatment until Monday, or when the hand had been treated on Thursday or Friday but became worse over the week-end and the patient did not attend for further treatment until Monday. These patients said that they did not like to bother their doctors over the week-end unless it was absolutely necessary; nor did they want to disturb their own week-end break. Works first-aid departments are often closed on Sundays, and sometimes the patient's doctor had no Sunday surgery, so that, in some cases, for the patient to have obtained medical attention on a Sunday would have required real effort.

The Materials Involved.—The large number of occupations involved and the variety of materials handled by the patients made the agents difficult to classify. In general the type of injury was more important than the agent causing the injury, and it seems that hand infections may develop amongst workers in any occupation where the workers are liable to receive small cuts and blisters. This is consistent with the bacteriological findings of Williams and Miles (1949), who showed that the source of the bacteria which cause wound infection is often the patient's skin or nose, and that there is little likelihood of contamination directly from the wounding agent.

First-Aid Facilities.—The fall in the industrial sepsis rate in recent years can be partly attributed to improved methods of treatment, the growth of the industrial health services and better first-aid facilities in industry, but unfortunately the standard of treatment and the provision of first-aid facilities is not uniformly good throughout industry.

The patients were asked to say what they thought of the first-aid facilities provided at their place of work, and most of them either had no particular comment to make or else they were very well satisfied with the first-aid attendance and facilities. Satisfaction was most often expressed by the miners and by people working for large firms. With one exception, all the patients in work covered by the regulations said that some kind of first-aid facilities

were provided, but there was not always a responsible person in charge, and even the trained attendants were sometimes criticized for the treatment they had given the patient. The exception was a builder's plasterer who said that there was supposed to be a first-aid box on the job, but when there was one it was usually empty. Often patients did not know of any person appointed to be in charge of the first-aid box, and in some firms the routine after receiving a small injury seems to be for the injured workman to help himself to the contents of the first-aid box, and he then either dresses the wound himself or else he finds a workmate or clerk to do it for him.

Prevention

There is no simple solution to the problem of industrial sepsis. Prevention can be considered from three points of view ; first, prevent the injury from occurring ; secondly, protect the worker ; and thirdly, improve the treatment.

The small injuries which become septic are brought about in a variety of ways, so that no one remedy can be very effective. Small metal filings are an obvious source of small puncture wounds, and to design machines which do not expose workers to injuries of this sort is a problem for the research engineer.

Since many of the injuries are caused by knocking the hand against something sharp, it should be possible to reduce the sepsis rate by eliminating the objects which may scratch and produce small injuries. Protruding nails can be knocked in or pulled out, rough metal edges filed down, and wire rope kept in good condition.

When tools are considered it is obvious that one way to reduce the danger of injury is by the correct use of the right tool. Workers sometimes use a defective tool as, for example, a hammer with a wobbly head, and this can lead to injury. Sometimes the tool is defective without the worker knowing about it, as in the case of a man who was injured by a piece of soft metal flying off the edge of a hammer head. The use of hand tools calls for the worker's full attention, and several injuries were caused by the worker allowing his attention to be distracted when he was using a hand tool. One point made by several patients was the importance of having a smooth handle on the tool. Constant rubbing against a rough, unvarnished, wood handle can easily cause a blister.

The use of protective clothing is a particularly relevant consideration, since many small injuries could be prevented if the worker wore safety gloves. There is still a certain amount of resistance to the use of all forms of protective clothing, and on the whole the patients did not take kindly to the idea of wearing gloves. This resistance can be attributed in part, no doubt, to the mind's dislike of any strange idea and to a natural conservatism by no means confined to industry. But the use of safety gloves is open to one special objection and this is that, unlike other articles of protective clothing, the use of gloves interferes with one very important function of the protected part. Safety gloves, if they cover the whole hand, impair the wearer's sense of touch. Many of the patients said that if they wear gloves they feel, literally, out of touch with the job because their hands are made to feel clumsy and incompetent, and they lose the feel of their fingers. Another objection was that gloves are dangerous because they are liable to catch in things, especially in moving machinery ; or they may slip in the process of throwing materials or goods as, for example, when a foundry worker is throwing metal into a furnace. Miners said that gloves make the hands too hot, and are unpleasant to wear if the pit is wet. Complaints were frequently made about the quality and the cost of the gloves offered. The gloves provided at work were said to be clumsy, ill fitting and without variety of style or size. The leather was said to be too hard, and hands are hurt when the rough part of the leather is on the inside of the glove. Also, the usual cost of leather gloves is about 8s. 6d. (although some firms issue them free), and it is said that they do not last for more than two or three weeks of hard wear. When due allowance has been made for valid reasons for not wearing safety gloves, it does seem that there is an unsatisfied demand for gloves of good material, made to fit the wearer, and suited to the job he does. Manufacturers of safety gloves in this country have put much thought into the problem of making good industrial gloves, and a wide variety of styles is made. Knowledge of the range of gloves available is not, perhaps, sufficiently widespread, and it is certain that there are bad industrial gloves on the market as well as good ones.

The third way of preventing industrial sepsis, as mentioned earlier, is by the improvement of first-aid treatment. One suggested method of doing this is to place the burden of responsibility on the worker, by instructing him to report every injury, however trivial, to the first-aid room. Williams and Capel (1945) made a study of this particular question, and they doubted whether the surgery treatment of all small injuries would materially reduce the incidence of industrial sepsis, because in the factories studied by them very few (1 to 2%) of the untreated wounds became septic. Furthermore, they estimated that

the surgery treatment of all trivial cuts—even if the workers could be induced to attend—would demand a five to tenfold increase in surgery staff and accommodation and would lead to an intolerable loss of working time. These conclusions are supported by the results of this study. Sixty-six of the patients (44%) would not have been helped by a system of reporting every injury, because these patients either had no known injury to report (30%), or else they did in fact report the injury straight away. Furthermore, the patients said that they were always cutting, scratching, and knocking their hands, and if all these injuries were reported an enormous amount of working time would be lost. As one man expressed it, " If I reported everything, I might just as well sit in the accident room all day."

It must be admitted that it is not always easy to provide good first-aid facilities, especially in the building trades where workers move about between sites, and in the shipyards where the layout makes it difficult for a first-aid room to be within easy access of all workers. Nevertheless, the evidence indicates that more might be done to improve first-aid facilities, and to educate first-aid attendants in the treatment of infections of the hand.

Discussion

The problem of wound infection is of national importance in view of its frequency and of its cost, both to the community and to the individual. It is very difficult to obtain even an approximate idea of the extent of sepsis in industry, but it is clear that although the arrival of antibiotics has greatly improved the outlook, a high proportion of industrial injuries become septic, and sepsis is responsible for a great deal of time lost from work. In addition, as far as hand infections are concerned, many patients with severe sepsis are left with some measure of disability (Robins, 1952).

The most comprehensive of the available figures are those given by the Chief Inspector of Factories in his annual reports (1950). These figures show that for 20 years or so before 1948 the proportion of compensation accidents due to sepsis varied between 10 and 12% of the total number of accidents. But the proportion of septic injuries has decreased steadily since 1948 and by 1951 the figure had dropped to 7·3%. In spite of this decrease, the figure is still high and in 1951 a total of 13,470 sepsis cases was reported and sepsis accounted for one death. These figures only include cases of industrial sepsis reported after sepsis had developed, and causing four or more days' absence from work. They make no allowance for injuries becoming septic after notification, or for cases of sepsis which have no history of injury and are not of proved occupational origin. The true incidence of industrial sepsis is probably much higher, and the figures will vary considerably in different occupations. In 1950 it was estimated that in the engineering industries in the Midlands sepsis caused between 10 and 30% of lost time accidents, and a corresponding proportion of time lost. Bull (1950), in a study of a light engineering factory, showed that in 1946 septic injuries caused 29% of all compensation accidents occurring in this factory, and 23% of the total time lost from work. The mean time-loss per injury for sepsis in this factory in 1946 was 25 days, but in 1948, after advances in treatment had been introduced, this figure was reduced to 17 days. In the present study the average time lost from work was about 24 days, but it should be remembered that for the most part these infections were well established and the subjects had to attend hospital. These facts make comparison between Bull's and the present series less illuminating than if both series had been of subjects attending factory medical departments.

The Ministry of National Insurance does not keep separate figures showing the amount paid out in benefits on account of industrial sepsis, but it is clear from the above figures that the cost to the community in terms of insurance payments made and production lost must be considerable.

Summary

The aims of the research were first, to find out how much time and money were lost through hand infections ; secondly, to assess the part played by occupational and social factors in the origin of infections of the hand ; and thirdly, to suggest how these infections might be prevented.

The patients interviewed were attending the hand clinic of the Department of Surgery in the Royal Victoria Infirmary, Newcastle-upon-Tyne. One hundred and fifty-one patients with infected hands were interviewed during the period from March, 1952, until December, 1952. Forty-five of these patients (30%) had no known history of injury. There was no selection of patients for interview ; during the weeks of interview all the new patients were seen.

Forty per cent. of the patients were either miners or engineers, and a further 22% were workers in transport or building or unskilled occupations. The remaining patients worked in a variety of occupations.

Sixty-five per cent of the injuries at work occurred as a result of knocking the hand against something. Other patients were usually hit by falling bodies, or blistered their hands by constant rubbing against tools.

Twenty per cent. of the patients with infected injuries had received treatment straight away, and 76% of the total number of patients reported for treatment either before the onset of symptoms or within three days of the onset.

The patients were usually off work for two to four weeks, and nearly three-quarters of the patients were back at work within a month. All but seven returned to their former employment.

Factors mentioned by the patients as possible part causes of their infections were poor general health, delay in seeking first treatment brought about by neglect or the intervention of the week-end, and inadequate first-aid facilities. The wounding agent was not considered important as a source of infection.

The prevention of trivial injuries, the use of hand tools, and the use of safety gloves are discussed. It is suggested that more might be done to improve the standard of first-aid treatment of hand infections. It is considered that it is not worth while to insist on the immediate treatment of every trivial injury.

I wish to thank Professor R. C. Browne for his advice and general help throughout the work, and also to acknowledge the statistical assistance given by Mr. H. Campbell and Mr. D. Newell. The work was made possible by the help and interest received from the staff and patients of the hand clinic of the Department of Surgery in the Royal Victoria Infirmary, Newcastle-upon-Tyne. I am also greatly indebted to Mrs. M. Berry for secretarial assistance, and to Mrs. D. Weightman for her help with the calculations.

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SOAP WRAPPERS' "JIG"

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The management of a perfume factory have been concerned for many years by the extensive rhythmical movements used by operatives in wrapping soap. These movements, which are widespread only in the soap department, became known as the "jig".

A field investigation was carried out to determine its effects on the operatives' health and on productivity.

There are individual differences in the movements but the term "jig" refers primarily to rhythmical swaying of the trunk backwards and forwards, and very rapid repetition of certain movements, such as folding the ends of the papers, with some extraneous ones, such as tapping and shaking the soap. There are some exceptions to this; in one case the chief sign consists in a rotation of the head. In new operatives the movements are reported to appear only gradually after training.

It is difficult to fix exact limits between "jig" and "not jig" because the distribution appears continuous, ranging from relative immobility of all muscles except those of arms and fingers, to a general response of the entire musculature. In extreme cases the movements are exaggerated and extensive, giving the impression of great activity performed in a spectacular, jerky manner. But if the "jig" could be objectively defined and measured the distribution would probably be positively skewed, fewer operatives having a high degree of "jig" compared to those with a low degree.

Description of the Job

The 15 soap wrappers sit facing each other in pairs (with one left over) at double desks which are placed in two rows of four on either side of a conveyor belt. The pairs are altered about once in six months. The wrappers are serviced with trays containing five or six dozen tablets on their left or right side, according to which way they are facing.

Soap is picked up with the left or right hand and placed on parchmentine (inner wrap) on the desk. Soap and parchmentine are then picked up and simultaneously the other hand picks up a board skillet (a strip of stiff paper) which is placed centrally on an outer wrap; the two hands are brought together, the soap and parchmentine being placed centrally on the skillet. A seam is made with a "druggist fold" and the soap is turned to wrap one end and then reversed to wrap the other. The soap does not rest on the desk when the ends are folded but is held up in front of the operative, slightly away from the body. Finally, the soap is placed on the belt and the other hand moves to pick up the next tablet. The time allowed for the whole cycle is 19 seconds.

Method of Investigation and Results

Since no objective measure could be devised, all wrappers were independently ranked from 1 to 15 for degree of "jig" by the supervisor, chargehand, and head girl. The mean of these three rankings was taken as an index of degree of "jig", the coefficient of concordance (w) being 0·88 ($P<0·001$).

An index of efficiency was obtained by taking the ratio of "standard hours" to "working hours". ("Standard hours" are equivalent to output, one standard hour being the amount of work which it is estimated should be produced in one clock hour. "Working hours" equal clock hours minus extra hours, *e.g.*, waiting time.)

The relation between "jig" and efficiency was investigated. The "jig" rank order was correlated with an efficiency rank order based on the mean of the previous three weeks' output. As predicted by the investigator, there was a positive correlation, Kendall's tau_b (Kendall, 1948) being +0·48 ($P=0·0139$). A similar correlation was calculated as a check between "jig" and mean efficiency for the first weeks of October, November, and December, 1953, tau_b being +0·52 ($P=0·0084$).

RANK CORRELATION BETWEEN "JIG" AND MEAN EFFICIENCY OVER THREE WEEKS*

"Jig"	1	2	3	4	5½	5½	7	8	9	10	11	12	13
Efficiency	1	3	2	7	5	6	10	12	8	13	11	9	4

$Tau_b = +0.48$, $P = 0.014$ (one tail)

* In all cases 1 is the maximum and 13 (or 15) the minimum of each variable.

RANK CORRELATION BETWEEN "JIG" AND MEAN EFFICIENCY FOR FIRST WEEKS OF OCTOBER, NOVEMBER, AND DECEMBER, 1953

"Jig"	1	2	3	4	5	6½	6½	8	9	10	11	12	13
Efficiency	1	3	2	6½	6½	5	9	10	11	13	12	8	4

$Tau_b = +0.52$, $P = 0.0084$ (one tail)

Each of these correlations includes one different operative, and one operative was excluded from both since a valid efficiency index could not be determined owing to her recent transfer away from, and back to, the department. With one exceptional case excluded these correlations would be considerably higher.

To ensure that these figures are not confounded by age or practice, tau_b was calculated between "jig" and (*a*) age and (*b*) duration of experience of soap wrapping. Neither of these correlations was significant, being +0·19 (P=0·35) and +0·14 (P=0·48) respectively.

RANK CORRELATION BETWEEN "JIG" AND AGE

"Jig"	1	2	3	4	5	6	7½	7½	9	10	11	12	13	14	15
Age	13	2	9	1	11	15	3	4	10	5	6	7	14	8	12

$Tau_b = +0.19$, $P = 0.35$ (two tail)

RANK CORRELATION BETWEEN "JIG" AND DURATION OF EXPERIENCE OF SOAP WRAPPING

"Jig"	1	2	3	4	5	6	7½	7½	9	10	11	12	13	14	15
Duration of experience of soap wrapping	9½	2	5	1	8	15	11	14	6	4	12	3	9½	7	13

$Tau_b = +0.14$, $P = 0.48$ (two tail)

Sickness records of the wrappers were compared with those of the 45 remaining operatives (banders, packers, etc.) in the soap department. Over the year 1953–54 the mean working days lost from certified sickness was 9·33 (S.D.=9·9) for the wrappers and 7·5 (S.D.=9·8) for the non-wrappers. In the category of respiratory diseases (including influenza and colds) the means were 7·1 (S.D.=9·2) for the wrappers and 3·3 (S.D.=5·5) for the non-wrappers.

Absence from all other causes was also compared between the two groups over the same period and the means were 5·2 (S.D.=5·8) for the wrappers and 4·9 (S.D.=6·3) for the non-wrappers.

The differences between the means were tested by Student's t test and no significant differences were obtained.

All wrappers were given a directed interview, the results of which are discussed below.

Discussion

Rhythm, as an aid to work, has been recognized in motion study since Gilbreth's *Principles of Motion Economy* (1923). But the term rhythm can refer to two different things : (*a*) the speed or rapidity with which repeated motions are made, and (*b*) the "beat" or variation of strain and rapid movement. Barnes (1949) observes that it is "most natural for the worker to fall into this [latter] kind of rhythm and that many kinds of work provide opportunity for the operator to accent certain points in a cycle of motion". Shaw (1952) stresses the role of rhythm as "one of the main characteristics of a good motion study pattern" and as providing "a definite focusing point or beat". Neither of these authors, however, gives much attention to rhythmical movements which are not part of the work cycle but constitute additions to the essential movements, although Barnes relates increase in muscular pressure and number of strokes to fatigue which breaks up the natural rhythm and disturbs coordination. Farmer (1921) states that individual rhythms, superimposed on the necessary ones, are introduced "either because motor control is weak, or because the ordinary movement involved in doing the task is of such a kind as to give no pleasure in its performance ; in this latter case another movement is introduced to compensate for the tiring effect of the necessary movement". He points out that "workers left to themselves may beat to an unnecessarily lengthy and complicated rhythm which may be the cause of many unnecessary movements, and which in turn may become a semi-automatic habit". To preclude these rhythms he advocates teaching rhythmic movements, of a circular rather than a jerky kind, in which "the terminal phase of the preceding movement naturally suggests the initial phase of the next". But the movements to be used are clearly limited by the requirements of the job and soap wrapping needs small, deft finger movements in various directions which would seem to be performed more naturally in a jerky, staccato manner rather than in a smooth, circular one.

Superimposed rhythms may be introduced to "synchronize with some physiological rhythm such as heart beat or breathing" (Farmer). They may

also be related in some way to the concept of "irradiation", a specific type of neuromuscular incompatibility associated with motor skill, which is defined as "progressive involvement of more and more tissue in aspects of activity that were originally more localized" and which is manifested "in spreading patterns of muscular tension and movement" (Bartley and Chute, 1947).

Self-estimation of "Jig".—Nine out of the 15 wrappers admitted using rhythmical movements of one kind or another (Nos. 1 to 8 and No. 13 on the rank order). Four out of the nine disliked making these movements and wanted to stop, including the two with the maximum "jig". Reasons for disliking it were impairment of efficiency and embarrassment (*e.g.*, "people think you are mad"). Three of the four who disliked it had tried hard to stop without any success. In one case (No. 6—head rotation) this seemed to make it worse, "You work quicker if you keep steady. I've tried to stop movements but the more I try to stop, the worse it gets—have given up trying to stop now". One (No. 13) was now quite reconciled to it. The following from Bartley and Chute (*op. cit.*) is interesting in this context:

> "Irradiation, although it represents a possible form of compensation for nerve and muscle tissue, in many instances represents for the individual a state in which he is less comfortable and less able to perform the task. The individual judges himself to be inefficient."

The five who liked the "jig" (Nos. 3, 4, 5, $7\frac{1}{2}$ and $7\frac{1}{2}$*) said that it helped them to work, *e.g.*, "the rhythm helps", "it just carries me along", and "it's better than sitting stiff and stark".

Work Situation.—It is postulated that the "jig" is related to variables in the work situation and in the operatives.

Imitation.—Strong evidence was gained from the interviews suggesting that imitation, conscious or unconscious, of skilled wrappers was related to the "jig" after training. Before presenting the evidence, methods of training new wrappers will be summarized.

Soap wrapping is considered by the management to be the most skilled of all the jobs in the factory, since it requires a high degree of finger dexterity and involves complicated movements which take some time to learn. The policy has been to make a really serious attempt to teach it, and, since it is apparently impossible to "pick it up" by sitting beside skilled wrappers, groups of three or four are instructed in the method, movement by movement, on a separate training belt in the same department. Once they are considered trained they are moved on to the skilled belt and allowed to develop their own individual ways of wrapping without correction.

In the absence of photographic studies, the correct method of wrapping was agreed upon by the methods department as that used by a particular chargehand who was not a "jigger".

The wrappers employed at the present time reported that this chargehand trained four of them, another chargehand (also without the "jig") trained five, two were trained by both, and two more were trained by both chargehands and a head girl. One of the wrappers (No. 1 on the "jig"), who was trained by three people, and another (No. $7\frac{1}{2}$ on the "jig") who was trained by both chargehands, spontaneously commented that they were confused by different methods. The period of training varied from six weeks to nine months.

Eight out of the nine operatives admitting the "jig" reported facing others with the "jig" when they were trained and only one reported facing an operative without it.

Four of the six who did not admit the "jig" reported originally facing those without it and two reported facing those with it, but in one case the movements were described as being only slight.

Seven of the nine reported developing the "jig" unconsciously ("it just came") and two reported that they were aware of developing it from sitting opposite or copying a girl with the "jig"; *e.g.*, "One wrapper told me to cut it out but we were also told to copy the girl opposite when we make a mistake" . . . "If the girl sitting opposite does it, then you would pick it up".

One wrapper (without the "jig") said: "We have to look down when sitting opposite a girl with a lot of movement". Another said: "All the girls watch 'X' (No. 3 on the "jig" and employed longest as soap wrapper). They say, 'Haven't you watched "X" wrap?'" A third said, "I sat opposite 'X' for a long time and that got me really moving".

Farmer (1921) re-trained younger workers in improved methods but when they saw older girls around them working in a different way and naturally producing more, they tended to drop the new methods and adopt the old ones again. But when training was started in a new room the young girls after three months of the improved methods, were, on average, producing 88% more than workers of the same standing in the original room. In another experiment a similar procedure was used but the trained young workers were then moved back into the original room with the consequence that the whole department, on average, started working with fewer

* Tied rank.

movements. There was, however, some reluctance to do so because " the new movements seemed so easy and some felt that if they adopted them they would not be working so hard as they ought to be ".

The above evidence, together with the fact that the " jig " is reported to develop slowly after training, suggests that training may not be sufficiently intensive or consistent to preserve the methods taught after moving to the skilled belt, and/or that training on a separate belt, but in the same room, still fails to eliminate the possibility of imitation, the effects of which appear later. It seems probable that liability on the part of new wrappers to imitate traditional methods varies inversely with the intensity and consistency of their training. Another possibility is that new wrappers imitated particularly two much older ones with 20 and 21 years' experience of soap wrapping (Nos. 2 and 4 on the " jig " rank order) owing to a prestige factor. The mean years soap wrapping of the remaining wrappers at the present time is 4·9 years. A prestige factor may also be related to efficiency as well as experience. The works manager thought that in 1949 some were following the methods of these older wrappers and others were following the methods of a young wrapper who was the most efficient and without any " jig ". When the latter left, the " jig " apparently spread to those who seemed to have been previously imitating her.

Posture.—Unlike most wrapping jobs, the arms are unsupported when the ends of the papers are folded round the soap and the backs of the seats are seldom used. This lack of support, together with the simultaneous and opposite reaching movements of the arms (one hand placing the soap on the belt and the other reaching for the next tablet), would probably induce some rhythmical sway.

Two wrappers spontaneously commented that the seats (which they can adjust themselves) were responsible for the swaying part of the " jig ". In one case, movements were considerably reduced by " finding a better seat " and, in the other, it was thought that if the seat were nearer the desk the movements would disappear, but this was not done because the operative concerned had become adapted to the habit : " it just carries me along ".

Speed of Work.—Evidence was gained from the interviews that the " jig " was related by the operatives to their efforts to pick up speed after training. This fact must be considered in connexion with the following brief history of the department since 1946.

Before 1946 payment was by straight piece work, except for trainees who had to earn more than a fixed minimum before they could be paid on this basis. In 1946 the standard hour bonus system was introduced and the rate was made easier because the " jig " conveyed the impression that the operatives were overworked. The old basic rate was 1s. 5d. and 2d. an hour bonus was expected but since all operatives earned the 2d. (and no more), it seemed highly probable that there was some history of rate cutting. The new basic rate was 1s. 7d. plus 33·3% for a normal worker. There was apparently still suspicion that rates would be cut because, although output eventually increased, it was a long time before the 33·3% was earned. In 1949 the work was moved to a different building and the operations were altered. The banding, which had been part of the job up to this date, was taken off and the conveyor belt system installed. At about this time there was real pressure, owing to de-rationing of soap. Time studies throughout the factory had shown that any under-production was not due to slowness in the operations but to the time wasted between them. Because of this the works manager pointed out to each wrapper individually how much more she could easily earn (about £1 a week) if wasted time was cut out. This resulted in higher output and more consistent efficiency. But the management still think that the wide range of earnings and the fact that two or three wrappers are bunched together at the top of the range indicate that they are not fully extended, even though, owing to the easy rate, they are earning, on average, higher wages than any other operatives in the factory.

In spite of the evidence of restriction, which was apparently unconscious and not acknowledged or agreed upon, two of these events—efforts to achieve rapidly the minimum in straight piece work (for the operatives now employed who worked under this system) and the encouragement to earn more by cutting out wasted time—acted as incentives. Two of the nine admitting the " jig " attributed it directly to the pressure of straight piece work and five (including the two above) attributed it to their effects to pick up speed after training, but one of these (No. 2 on the " jig " ranking) considered the impression of increased speed with " jig " was illusory, " You think you are doing it more quickly by swaying . . . but the less you move, the more you get done ". It is perhaps significant that Nos. 1 and 2 on the " jig " rank order, who both wished to be rid of it, were among the fastest, Nos. 1 and 3 on the efficiency rank order.

The positive correlation between " jig " and efficiency only means, of course, that, under present conditions, working with pronounced rhythmical

movements is relatively more efficient than working without them. It implies neither an absolute nor a causal relation between these variables. Farmer, however, cites some evidence to show that, if the idea of output comes to assume more importance than methods, the increased rate of working may result in movements which are too numerous or extensive. But under optimal conditions during training, such as total absence of the possibility of imitation and consistent attention to methods, the same evidence suggests that high efficiency could be reached without any superimposed rhythms.

Operatives.—It is hazardous to generalize from so few instances but it seems likely that there is some factor in the operatives which accounts for resistance to the "jig" under conditions which otherwise appear to induce it. The young operative, previously mentioned in the discussion of imitation, was, in the words of the works manager, "undoubtedly the fastest wrapper we have ever had" and "did not move a muscle other than her fingers". In 1949 she was deliberately placed opposite one of the high "jiggers" (No. 3 on the "jig" and employed 21 years as a wrapper) with the result that she remained immune to the "jig". The speed of the "jigging" wrapper, however, increased considerably, without lessening the extent of her "jig". At the present time there is only one really discrepant case, No. 4 on the efficiency rank order and No. 15 on the "jig", but she also recalled originally facing one with the "jig". Both these cases were apparently "jig resistant", in spite of the fact that they were fast workers and fully exposed to the possibility of imitating it.

It is possible that these individual differences in degree of motor control, and those which Farmer noted, are correlated with metabolic or psychological variables of wider generality.

Summary

The management of a perfume factory have been concerned for many years by the extensive rhythmical movements used by their 15 soap wrappers. These movements, which became known as the "jig", range in different wrappers from relative immobility to a general response of the entire musculature, giving the impression of a high rate of spectacular activity. The movements are not conspicuous in any other group in the factory.

A field investigation was carried out to isolate some of the principal variables.

Significant positive correlations were obtained between degree of "jig" (as rated by three independent judges) and efficiency.

No significant correlations were obtained between degree of "jig" and age or duration of experience of soap wrapping.

No significant differences were obtained in days lost from (*a*) certified sickness and (*b*) all other causes, between soap wrappers and other operatives in the same department.

Evidence was adduced to suggest that the "jig" is related to (*a*) liability of newly trained operatives to imitate rhythmical movements in skilled ones, (*b*) posture, *i.e.*, the physical stance of the operative in relation to the work, (*c*) efforts to increase speed, whether self-induced or induced by others, and (*d*) a possible factor of resistance or susceptibility to "jigging" which may interact with the other variables.

An experimental investigation is needed to test these hypotheses, if and when further instances of the phenomenon are observed, and to establish what causal relations exist between the above variables.

Since this investigation was concluded, the works manager has reported that work is in progress on improved methods of soap wrapping.

I should like to thank the management of the firm, particularly the works manager and the operatives concerned, for their help and cooperation in this research.

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A SIZE-SELECTING SAMPLER FOR AIRBORNE DUST

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It has long been known that airborne dust often differs markedly in composition from dust which has settled on the ground, and this in turn differs in composition from the parent substance from which the dust was produced.

This variation in composition is related to variation in particle size, and continues even within the size range of airborne dust. For instance, Drinker and Hatch (1936) quote an example where the free silica content of an airborne foundry dust varied from 72·3% for particles over 10 μ in diameter, 28·2% between 5 μ and 10 μ, 22·7% between 2 μ and 5 μ, down to only 3·3% below 2 μ.

It has also been known for many years (McCrae, 1913; Watkins-Pitchford, 1916) that the dust retained in the lungs consists almost entirely of particles below about 7 μ in average diameter. More recent theoretical and experimental studies (Findeisen, 1935; Davies, 1949) have shown that the failure of large particles to penetrate and be retained in the lungs is related to their high settling rate in air.

It is evident then that any chemical analysis of airborne dust which is to be relevant to pneumoconiosis must be confined to that fraction of the dust which consists of particles of what may be called for convenience " respirable " size. This conclusion has been recognized by a number of workers, and they have attempted to comply with it by separating the respirable fraction from the sample after collection, either by liquid sedimentation or by air elutriation. The former method is unsatisfactory since the different densities of the various ingredients will cause a greater difference in settling rate in liquid than in air. The method is, moreover, open to another objection, which also applies to air elutriation, namely that dust in the air is nearly always aggregated to some extent (Watson, 1949) and the aggregates will have a settling velocity very different from that of their constituent particles. If the dust is collected and then re-dispersed in liquid, it will be largely disaggregated, and even if re-dispersed in air its original state of aggregation will not be restored, so that it will not be separated into true respirable and non-respirable fractions.

Apart from these objections, the process of separation after collection is laborious and to be avoided if possible, but until recently no easy and satisfactory method of separation while sampling was available. The most obvious device, a vertical elutriator, such as is used commercially for air separation of powders (Haultain, 1937) can be shown to be impracticable owing to the very large size of chamber needed for the volumetric sampling rate which is usually required (Walton, 1954).

Another obvious possibility, the cyclone, is open to the objection that the dust is exposed to a process of attrition which may break down aggregates; moreover, the behaviour of a cyclone is critically dependent on its design.

Recently Walton (1954) has investigated the whole question of elutriation and has shown that a simple horizontal elutriator has many practical advantages and is moreover capable of giving as sharp a cut-off as any other elutriation process. The process of separation it uses is closely similar to that occurring in the respiratory tract, and although the shape of the cut-off curve is somewhat different from that currently attributed to the respiratory tract (Davies, 1952), the difference is not great and, owing to the general constancy of size distribution of dust particles in this size range (Wynn and Dawes, 1951), it is small in importance compared with the necessity of eliminating the bulk of the non-respirable dust.

The fundamental principle of a horizontal elutriator is that dusty air is passed through a horizontal duct at such a velocity that particles which it is desired to capture will settle on the floor of the duct before they reach the end. Particles of lower settling rate will, to a greater or lesser extent pass through the duct; those which were initially near the floor being captured, and those higher up passing through, the proportion doing so varying

inversely as their settling rate, which in turn varies as the square of their diameter, for particles of the same shape and density. Thus if an elutriator is designed, as suggested by Hamilton and Walton (1952), to capture 50% of particles 5 μ in diameter, it will capture only 2% of 1 μ particles but will capture 100% of particles 7·07 ($5 \times \sqrt{2}$) μ in diameter. So long as the flow is streamline and not turbulent, the time taken by a particle of given settling velocity to fall from the top to the bottom of the duct will be proportional to the height of the duct ; and the time taken for the particle to traverse the length of the duct will be proportional to the air velocity. This in turn will be proportional to the volumetric flow-rate and the cross sectional area of the duct. If the height of the duct is increased, but its breadth kept constant, the time taken for a particle to fall from the top to the bottom will be increased, but the air velocity will be decreased proportionately, so the chance of a particle passing right through will not be affected. Thus, for a given volumetric flow rate the performance of a horizontal elutriator is independent of its height, and depends only on its length and breadth, *i.e.*, the area of its floor. This area can be very easily calculated : if the volumetric flow through the elutriator is Q, and the terminal velocity of the largest particle which it is desired to capture 100% is V then the area of the floor required $= \frac{Q}{V}$.

The floor area can be arranged in any convenient way, either as a single long wide duct, or as a stack of shorter and narrower ones, so long as care is taken to ensure that flow will be streamline. When a stack of ducts is used attention must be paid to an important practical point which is not mentioned by Hamilton and Walton.

The flow through a flat horizontal duct at a given pressure depends on the cube of its height (Goldstein, 1938) and therefore some care is needed in its construction if it is made fairly shallow, which is desirable for the sake of compactness. For example, if the height of one duct is increased by 25% and the height of the adjacent duct decreased correspond-

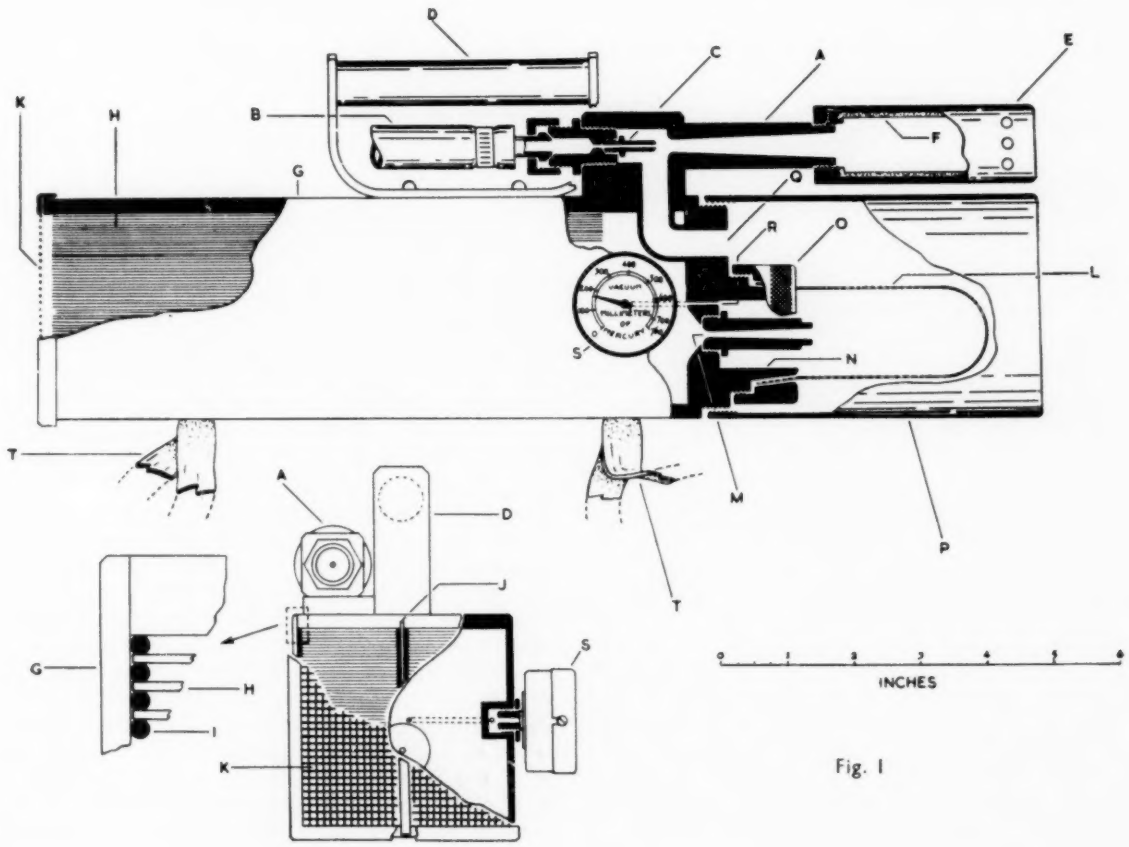

Fig. 1

ingly, the flow through the former will be nearly doubled while that through the latter will be nearly halved, although the actual dimensional error in, for example, our model would be only 0·008 inches. The corresponding change in the cut-off will be from 7 μ to about 10 μ and 5 μ respectively. The effect on the behaviour of the elutriator as a whole will, however, be greater than this, since there will also be a proportionate loss of finer particles in the shallower duct which cannot be balanced by a corresponding increased penetration through the other because penetration is already nearly 100%.

In the instrument to be described, an elutriator of this type has been fitted to an improved form of the "soxhlet" thimble sampler described by Griffiths and Jones (1940).

Description of Instrument

The complete apparatus, which has been given the portmanteau name of "hexhlet", is shown diagrammatically in Fig. 1. It is made up of four components: the horizontal elutriator, a critical orifice to control the air flow, a "soxhlet" thimble for collecting dust, and a compressed air ejector to provide suction.

The elutriator consists of a rectangular box (G) made of aluminium alloy in which are stacked two banks of 58 aluminium plates (H) 0·020 in. (0·5 cm.) thick and 0·032 in. (0·8 cm.) apart separated by a partition (J), forming 118 ducts. The plates are 1·42 in. (3·55 cm.) wide and 10·06 in. (25·1 cm.) long, so that the total floor area of the elutriator including the floor of the box between the end of the plates and the critical orifice is about 1,690 sq. in. (10,903 sq. cm.).

The plates are separated by lengths of steel wire (I) as shown in the enlarged section, and the whole unit is assembled by stacking the plates and wires in a box and then clamping and screwing the top on. This method of construction (which was suggested by Mr. A. Hyett) gives excellent uniformity of duct height, and is at the same time much easier to carry out than the more obvious procedure of fitting the plates into slots in the side of the box. Ordinary rolled aluminium sheet is sufficiently flat for the purpose. Plastic sheet is unsuitable because of electrostatic effects.

The front end of the stack of plates is close to the end of the box and is protected by a stout wire mesh grid (K). The rear end is about 1½ in. (3·75 cm.) from the end of the box, into which is fitted the critical orifice (M) leading to the inside of a "soxhlet" thimble (L). The purpose of this space is to prevent channelling of flow down the elutriator owing to undue proximity of some of the ducts to the orifice.

The vacuum gauge (S) which is connected to the inside of the "soxhlet" by the passage (R) enables the flow through the instrument to be checked at any time while in operation.

The "soxhlet" thimble is fitted on to a conical nozzle (N) to which it is secured by the knurled screw ring (O), and is enclosed in a case (P) which is connected through the elbow connexion (Q) to the air ejector (A). The air from the latter passes into a silencer (E) which is lined with felt (F).

The ejector is fitted with a short length of hose (B) which can be coiled up and secured with the two straps (T) so that the complete instrument can be carried by the handle (D) as shown in Fig. 2.

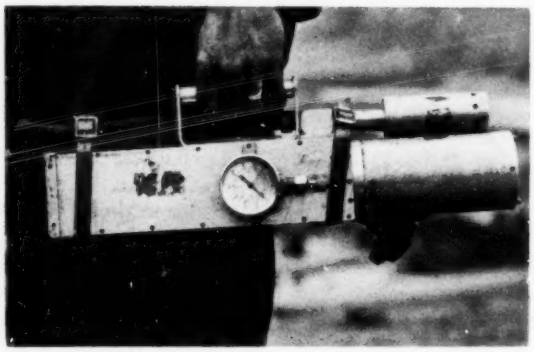

Fig. 2

Performance

The Elutriator.—The elutriator was designed to collect 50% of particles of unit density 5 μ in diameter at a volumetric flow-rate of 100 l./min. Its performance was checked by means of a cloud of monodisperse "pyrex" glass spheres of density 2·25 produced by feeding powdered "pyrex" glass by means of a dust feed mechanism (Wright, 1950) into the air supply of an air acetylene flame. The cloud consisted almost entirely of single spheres varying in size up to 15 μ in diameter.

A preliminary test was carried out by placing glass cover slips at the front and rear ends of the plates at intervals all the way up the stack. This test showed good uniformity of cut-off and enabled a relative penetration curve to be constructed. In order to obtain an absolute penetration curve the following procedure was adopted (Fig. 3).

A hole ⅜ in. in diameter was cut in the bottom of the case, between the end of the plates and the critical orifice, and was covered with a metal disc (U) about 2 in. in diameter, pivoted to one side of the hole.

A ¾ in. circular cover slip (V) was let into the upper surface of the disc, to one side of its centre, so that when the disc was suitably rotated the cover slip could be brought under the hole. Arrangements were made to block up the critical orifice inside the case P by means of a plunger (W) and rod (X) passing through the end of the case. In this way the space at the back of the elutriator case was turned into a sedimentation cell.

A sedimentation cell of the same height as the elutriator case was placed close to the front end of the instrument, and the whole assembly inserted in a

chamber in which the cloud of spheres was being generated.

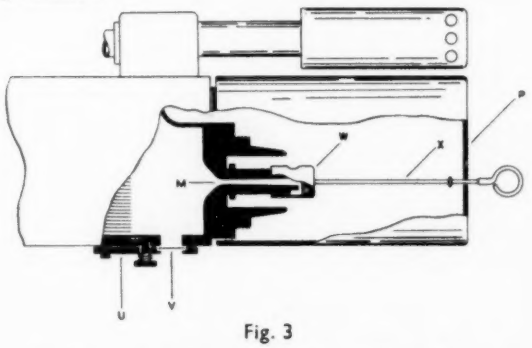

Fig. 3

The " hexhlet " was run for five minutes and then the flow was cut off sharply by means of the plunger (W), and at the same time the cover slips under the case and under the sedimentation cell were exposed. Time was allowed for spheres down to 0·5 μ to settle and the process was repeated until examination of the " hexhlet " cover slip showed that a sufficiently dense deposit for counting had been obtained.

Total and differential counts were then made on the two samples, and the results combined to give the penetration curve shown in Fig. 4, where it is compared with the theoretical curve for a cut-off of 50% at 3·3 μ diameter for glass spheres (equivalent to 50% at 5 μ for unit density).

The effect of loading the plates with coarse dust was determined by running the instrument in a heavy laboratory coal dust cloud, containing particles up to 100 μ in diameter, until 2 g. of " respirable " dust had collected in the filter. A subsequent test in the glass sphere cloud showed no change in the cut-off size. This is in conflict with the statement of Dawes (1954) ; the discrepancy may be due to the fact that in this model the ducts are so shallow that there is no possibility of turbulent flow being produced (Reynolds Number = approximately 25).

The Critical Orifice.—The purpose of this is to maintain a constant volumetric flow-rate in spite of variations in compressed air pressure and the increasing resistance of the filter as dust is collected. Constancy of flow-rate is essential in order to maintain constancy of cut-off, and the use of a regulator and gauge such as that described by Watson and Morris (1952) would entail too much supervision.

The behaviour of a critical orifice is due to the fact that the flow through it depends only on the upstream pressure, and is independent of the downstream pressure, once the air velocity through the orifice reaches that of sound (Hartshorn, 1918). In a vacuum system such as this the upstream pressure is atmospheric and therefore substantially constant in a given place. It is, however, necessary that the orifice should be upstream of any source of varying resistance in the system, which in this case is the filter, so all the dust collected has to pass through the orifice. Since this dust is all of very fine particle size it has almost no abrasive power and does not wear the orifice appreciably, nor does blockage occur. The disadvantage of a critical orifice is that it consumes a good deal of power (about $\frac{1}{10}$ h.p. in this instrument). At the suggestion of Dr. C. N. Davies the orifice was therefore fitted with a tapered outlet which gives a substantial recovery of pressure head (Hartshorn, 1918), so that critical flow is obtained with only 100 mm. of vacuum, instead of the more usual 350 mm. (Perry, 1941). The diameter of the orifice was calculated from the formula given by Perry (1941) for a flow of 100 l./min. The orifice was then drilled a little undersize (0·14 in.) and reamed out until it gave the correct flow. Clogging of the filter or lack of air pressure is indicated by the vacuum gauge ; if the vacuum falls

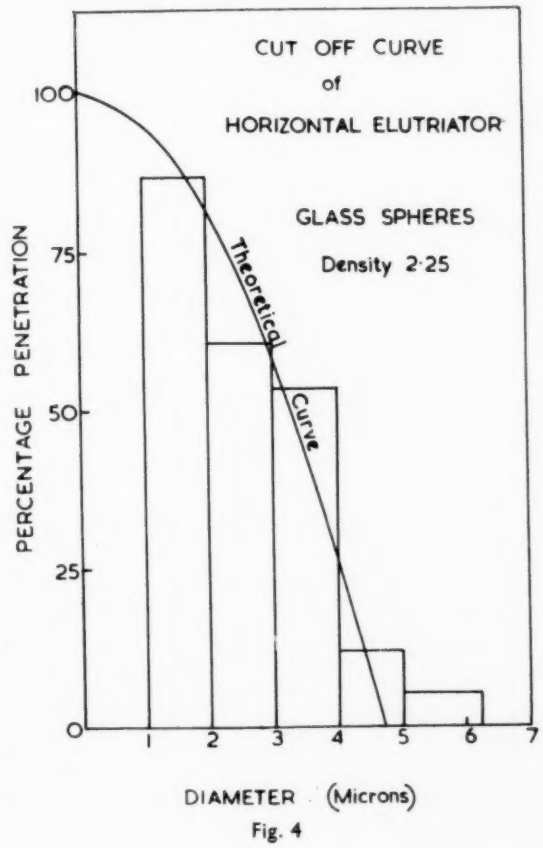

Fig. 4

below 100 mm. Hg with an adequate air pressure, the filter must be changed or the cake of dust dislodged.

Up to 1 g. of " respirable " dust can usually be collected in the filter before this is necessary.

The Soxhlet Filter.—As pointed out by Watson and Morris (1952), about 100 mg. of dust is permanently trapped in the filter, whose resistance is thereby also permanently raised. The loss of dust might be materially reduced by " pre-clogging " the filter with a suitable inert dust.

The Air Ejector.—This is similar in design to that used by Watson and Morris but the jet (C) is only $\frac{3}{32}$ in. in diameter and the rest of the device is scaled down accordingly. The best position of the jet in relation to the throat was determined by experiment. The ejector will give a critical flow at 100 l./min. through a clean " soxhlet " filter with a compressed air pressure of 25 lb. per sq. in. or more. As most compressed air supplies give a pressure of 60 lb. per sq. in. or more there is ample margin to allow for the build-up of dust on the filter.

Coal dust is collected at a rate of about 1 g. in an eight-hour shift at an average concentration of 850 particles/ml. (1·0–5·0 μ).

The felt-lined silencer has a striking effect in reducing the otherwise very offensive noise made by the ejector.

The instrument in its final form has now been in routine use in this Unit for six months, and has given satisfactory results. Its weight of 10 lb. makes it reasonably portable, but the need for a compressed air supply limits its range of usefulness. Where compressed air is not available an electric vacuum pump can be used, though, owing to the resistance of the critical orifice and the filter, a pump of about $\frac{1}{3}$ h.p. is required. For use in this way, the silencer is removed and the vacuum pipe connected to the outlet of the ejector, the inlet being closed by means of a blanking nut instead of the hose connexion.

In a mine the instrument is usually hung from the roof by cords, but any convenient method of support is satisfactory so long as care is taken to keep it reasonably nearly horizontal. The effect of deviation from the horizontal is to decrease the effective settling rate of the particles on to the plates, and therefore increase the cut-off size. This effect is small, since it depends on the square root of the cosine of the angle of deviation from the horizontal. An angle of 5° (which is easily appreciated) produces an increase in cut-off size of only $\frac{1}{5}$%.

The instrument tends to build up a static charge, so it is essential to earth it by means of a metallic connexion to a water or compressed air pipe.

Summary

The composition of airborne dust is liable to vary with particle size.

Only particles less than about 7 μ in average diameter are retained in the lungs long enough to cause pneumoconiosis. Samples of airborne dust for analysis in connexion with pneumoconiosis must therefore be free of particles larger than this. The separation of these particles should be carried out during the process of sampling.

An apparatus for collecting bulk samples of airborne dust is described in which a horizontal elutriator is used to separate off the oversize fraction while sampling, the " respirable " fraction being collected in a " soxhlet " thimble filter. A compressed air ejector is used to draw air through the sampler, and a critical orifice controls the flow.

The theoretical principles on which the design of the sampler is based are discussed, and the method of testing its performance is described.

The instrument was developed and the first model made in this laboratory and is the combined product of many workers to whom I am much indebted. Thanks are due especially to Mr. W. H. Walton and Mr. R. J. Hamilton, of the National Coal Board's Central Research Establishment, for advice on the design of the elutriator. The final model was constructed by Mr. V. Gubb and the tests of the elutriator and critical orifice carried out by Mr. N. E. Bevan. Mr. H. S. Wolff designed the silencer, and also suggested the name " hexhlet ". Mr. W. H. Roberts prepared the drawings.

Messrs. C. F. Casella & Co. Ltd., Regent House, Fitzroy Square, London, W.1, will be the makers.

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A FOLLOW-UP STUDY OF PNEUMOCONIOSIS IN AN IRON FOUNDRY AND SOME INVESTIGATIONS INTO THE EFFECT OF FOUNDRY DUST IN THE LUNGS

BY

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In a survey of health and environmental conditions in the Butterley Foundries (Keatinge and Potter, 1945) one of the principal health risks to which the workers were exposed was found to be pneumoconiosis, and it was estimated that the potential dust risk of fettlers was many times greater than that to which other workers in the foundries were exposed. Sixty foundry men, divided into broad occupational groups, five fettlers, 31 moulders, 24 others, were submitted to *x*-ray examination of the chest. Two out of the five fettlers examined were affected in comparison with only eight out of the 31 moulders.

Since the publication of this survey a number of other inquiries have been made into the health of foundry workers and the environmental conditions in foundries (Eskildsen, 1949; Gordon, 1950; Vigliani, Parmeggiani, and Zanetti, 1948; Zanetti and Dompè, 1950) but the most extensive has been that undertaken by McLaughlin (1950), in which 2,767 people were examined. McLaughlin and his colleagues however found that in the iron foundry the moulder as compared with the fettler was exposed to a greater risk of silicosis probably due to the use of silica parting powders.

Although several surveys have been made of the health of foundry workers, few follow-up studies appear to have been carried out in Great Britain. Since the last study of the Butterley Foundries was published nearly 10 years ago it was felt that a further survey of the incidence of respiratory disease amongst those examined on a previous occasion might prove instructive; in considering the findings of the present survey, it must be borne in mind that it is iron-founding alone which is carried out at Butterley.

There are three foundries at Butterley: No. 1 Foundry produces small, medium, and light castings, on a semi-mechanized basis; No. 2 Foundry makes large castings of a general nature; and No. 3 Foundry very light castings on a fully mechanized unit. More than 200 workers are employed in the foundries, of whom 20 are engaged in fettling, 50 in moulding, 16 in core-making, and the remainder in other work. The work done is representative of many branches of iron-founding, and the building and general conditions are of a kind very usual in the industry.

The dust environment in the Butterley Foundries has not altered materially since the previous survey was carried out and is comparable with that recorded in other iron foundries by McLaughlin (1950). Examination of the dust (at Sheffield University) showed obvious large particles, and a fine fraction was separated by suspension in tap water and decanting into a large filter, after the larger particles had sedimented. Samples of the dust after separation of this fine fraction showed that it contained 35 to 36% of total silica, and 38% of iron, (reckoned as Fe_2O_3): chemical analysis (Trostel and Wynne, 1940) gave the percentage of free silica as 24·8% and *x*-ray analysis gave a figure of 18·5%.

Health Studies

Fifty-three people examined in 1943 and 1944 are still working in the Butterley Foundries and their ages range from 28 to 71; the mean age is 45·3 years. These workers fall into the following broad occupational groups; 41 moulders, eight fettlers, and four core-makers. The incidence of respiratory disease experienced by these people has been assessed by examining their individual record cards which show the duration of each absence due to sickness or injury, clinical examinations, and radiography of the chest.

Absence Due to Respiratory Disease.—A careful note of the amount of time lost by each worker has been kept since 1943 and the nature of the sickness or injury has been recorded when absence from work has been due to these causes.

Although respiratory disease has been the greatest single cause of sickness absence in the period from 1944 to 1952 inclusive, relatively few cases of serious chest affections have been recorded amongst these workers. Thus, absence due to bronchitis took place only on seven occasions in all these years, accounting for an annual average loss of time of no more than 0·34 days per worker. There were three cases of pneumonia giving a loss of time averaging for each year 0·17 days per person and there was no absence as a result of pulmonary tuberculosis. Three employees lost no time due to sickness or accident during the nine years under review.

Clinical Examination.—Although workers engaged in cleaning castings are submitted to annual radiography of the chest, and young persons up to the age of 18 and workers of 65 and over undergo periodic medical examinations, these are not carried out as a routine measure in all employees. Their health is, however, carefully supervised and a review is made of the physical state of those returning to work after absence due to sickness or injury. A clinical investigation is not necessarily required in all cases, but 18 of these 53 workers had been examined during the two years before this survey. Abnormal physical signs due to respiratory disease were found in only three people and all of them were over 60 years of age. Two of these men complained of shortness of breath and cough, and on examination the breath sounds were distant and crepitations were heard at the bases. In another worker the clinical findings were similar and electrocardiography showed the presence of a right bundle branch block.

Radiography of the Chest.—Of the 53 men, four were unwilling to submit themselves to further *x*-ray examination of the chest; the films of these four workers taken in 1943–44, however, had at that time been regarded as normal and the incidence of respiratory illness amongst them since that time had been negligible. The *x*-ray classification used has been that adopted by McLaughlin (1950).

Category I = Normal
Category II = Early reticulation
Category III = Reticulation
Category IV = Nodulation and/or massive shadows

All the films were read independently by three observers, and there was substantial agreement on the readings between all of them. However, where there has been disagreement, the majority view has been taken and in the few cases in which each observer has given a different reading, the mean has been taken.

Table 1 gives the *x*-ray findings in the present survey of the 49 members of the group of 53 men previously surveyed in 1943–44 and the distribution is given by *x*-ray category, age, and length of exposure in years. Table 2 shows the *x*-ray categories by occupational groups. The *x*-ray findings are in all but three cases identical with those seen in the 1943–44 films. In two instances there had been progression from Category I to Category II, and in one from Category I to Category III.

TABLE 1
X-RAY FINDINGS IN FOLLOW-UP STUDY OF WORKERS EXAMINED IN 1943–44

Age (years)	*X*-ray Category	Length of Exposure in Years			
		10–19	20–29	30+	Total
15–29	I	2	—	—	2
	II	1	—	—	1
	III	—	—	—	—
	Total	3	—	—	3
30–39	I	10	5	—	15
	II	2	—	—	2
	III	1	—	—	1
	Total	13	5	—	18
40–49	I	1	1	5	7
	II	1	2	2	5
	III	—	—	1	1
	Total	2	3	8	13
50+	I	1	—	7	8
	II	—	—	6	6
	III	—	—	1	1
	Total	1	—	14	15
Total	I	14	6	12	32
	II	4	2	8	14
	III	1	—	2	3
	Total	19	8	22	49

TABLE 2
OCCUPATIONAL GROUPS AND *X*-RAY FINDINGS OF 49 MEN EXAMINED IN FOLLOW-UP STUDY*

Craftsmen	No. at Risk	Category I	Category II	Category III	Total
Moulders	41	28	10	1	39
Fettlers	8	1	3	2	6
Coremakers ..	4	3	1	—	4
Total	53	32	14	3	49

* Four men out of the 53 at risk were not radiographed again for various reasons.

Laboratory Investigations

In November, 1952, a moulder aged 36 years who had worked in the Butterley Foundries for

FIG. 1.—Section of lobe of the lung of an iron moulder (natural size).

22 years died as a result of an accident at work. From 1943 his health had been good and during these nine years he had been absent on only 33 days (11 days for a carbuncle on the wrist, 17 days for fibrositis, and five days for a "chill"). In 1944 radiographs of the chest had shown only increased linear markings; unfortunately no recent *x*-ray examination had been made. A necropsy was performed by Dr. I. MacKenzie and the lungs were sent to Sheffield University for further examination. When received, the lungs were largely hardened by formalin but it was possible to distend one lobe for large sections. Macroscopically there was definite but not severe focal emphysema with small, palpable, spidery, black nodules; the hilar lymph nodes were moderately enlarged, very black, and moderately firm. A large section (Fig. 1) of one lobe showed some bullous emphysema with pneumoconiosis. Histological examination (Fig. 2) showed focal emphysema and early collagenous fibrosis in aggregates of pigment alongside bronchioles and small arteries; incinerated sections showed that much of the opaque pigment was iron. Chemical analysis of the lungs after fixation in formol-saline gave the following percentages of dry weight; ash 3·07, total silica 0·54, free silica 0·33, iron (as Fe_2O_3) 0·37.

FIG. 2.—Small pneumoconiotic nodule with associated focal emphysema. H&E. × 24.

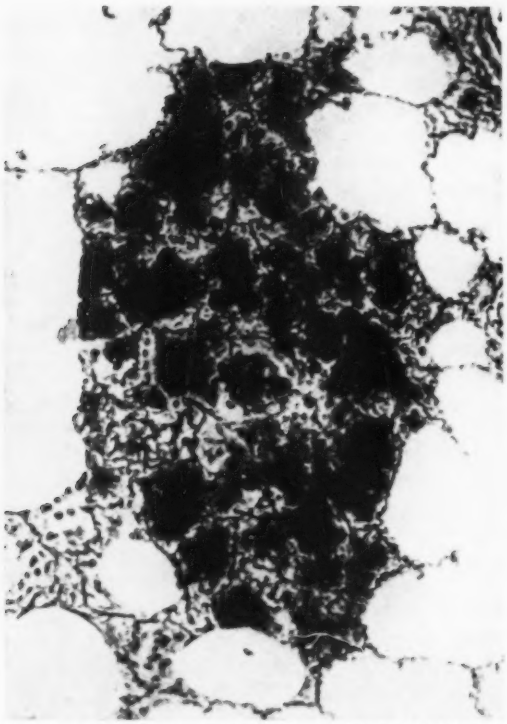

FIG. 3.—Rat 52/16. Aggregate of cells containing inhaled foundry dust. Reticulin stain. × 190.

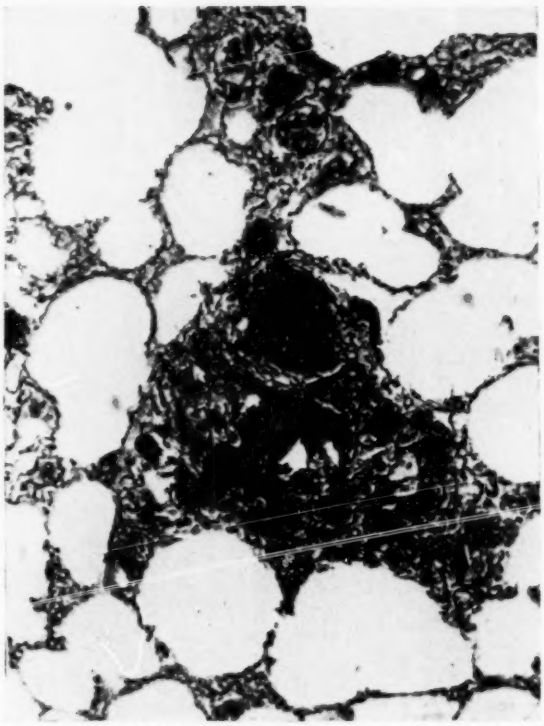

FIG. 4.—Rat 52/26. Dust aggregates after injection of a suspension of dust. Reticulin stain. × 190.

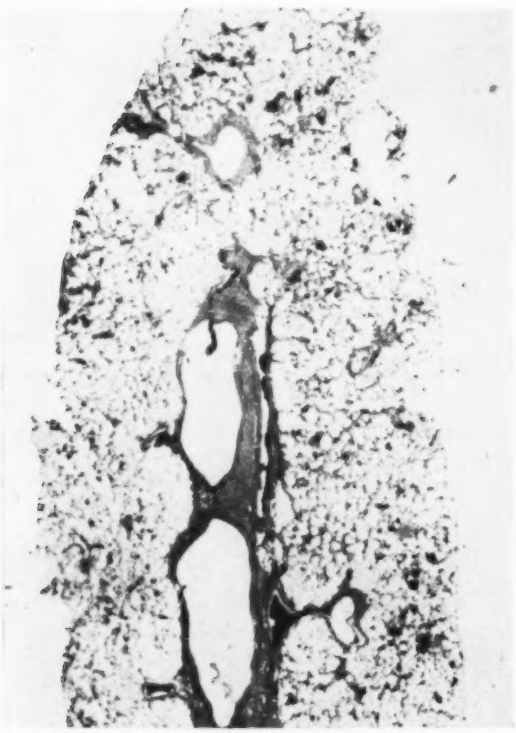

FIG. 5.—Rat 52/16. Inhaled foundry dust. Hx. E. × 8.

FIG. 6.—Rat 52/26. Injected foundry dust. Hx. E. × 8.

FIG. 7.—Rat 52/16. Inhaled dust. Radiograph of lung. × 8. (The areas of collapse in the lower part of the lung are artefacts produced by faulty technique in preserving the specimen.)

FIG. 8.—Rat 52/26. Injected dust. Radiograph of lung. × 8.

The findings in this moulder's lungs showed that there is, or was, a risk of pneumoconiosis in the foundry, but are not of course evidence of the degree of such risk. The pneumoconiosis in this man was perhaps sufficient to produce minimal symptoms but there is no evidence that it had done so.

Fine dust from Butterley Foundries, 50 mg., suspended in 1 ml. saline, was injected intraperitoneally into each of two rats, and 50 mg. of a very pure rouge (Fe_2O_3) into another pair of animals. Eight months later no fibrosis was detectable around aggregates of rouge, but slight fibrosis with an occasional foreign body giant cell was found in relation to aggregates of foundry dust. The two dusts were, however, not strictly comparable in particle size, the foundry dust containing particles larger than any in the rouge.

A group of 24 young piebald rats was exposed to a dense cloud of foundry dust in a chamber for approximately 40 hours weekly for 37 weeks, and the seven survivors killed after a further five weeks. The thoracic contents were removed with the lungs in an inflated state, fixed in formol-saline, radiographed after 24 hours, and then sectioned. A further group of rats was anaesthetized with ether and given injections through the larynx of a suspension of dust

FIG. 9.—Normal rat. Radiograph of lung for comparison. × 8.

in sterile physiological saline : 200 mg. of dust was injected in four doses during four weeks, and six animals were killed after six and a half months. The thoracic contents were fixed in formol-saline, radiographed, and sectioned.

Microscopical examination showed aggregates of dust related to terminal bronchioles with no associated collagenous fibrosis and only slight or doubtful increase of reticulin fibrils (Figs. 3, 4, 5, and 6). Radiographs of the lungs showed, however, distinct shadows corresponding with the aggregates, larger and coarser in the injected animals than in those that had inhaled the dust (Figs. 7, 8, and 9). These shadows are presumably due to iron oxide and not to fibrosis. (It is interesting to note that the control radiograph of a normal rat lung shows a reticular pattern.) That this dust, in spite of its fairly high content of free silica, did not produce fibrosis in the rats' lungs is not unexpected. These animals do not commonly show fibrosis unless the proportion of silica is very high ; negative results in laboratory animals cannot safely be taken as applying to man.

Conclusions

Although the low incidence of respiratory disease amongst the workers in the Butterley Foundries examined in this follow-up study and the absence of evidence of progression in the *x*-ray films of all but a few men suggest that environmental conditions in these foundries do not carry an undue risk for the worker, it must be emphasized that it cannot necessarily be assumed that similar conditions obtain in all iron foundries.

Although histological studies of the lungs of the moulder who died as a result of an accident at work showed evidence of focal emphysema and early collagenous fibrosis, much of the opaque pigment seen in the lungs was undoubtedly iron. Moreover, analysis of the foundry dust showed that a high proportion of it too was iron, and in addition dusting experiments on rats with foundry dust failed to elicit fibrosis although radiographs of the lungs showed distinct shadows presumably due to iron oxide. While it would be unsafe to read too much into these findings, there is certainly some evidence to suggest that the radiographic appearances seen in the films of these foundry workers may be due as much to the presence of radio-opaque dust in the lungs as to fibrosis. Hamlin (1947), as a result of a study of workers in an iron foundry and after dusting experiments with guinea-pigs, rats, and rabbits, considered that *x*-ray observations in his group of workers represented siderosis. Kettle (1932) showed that a coating of iron on quartz particles has an inhibiting effect on their fibrosis-forming properties in the lung, and the presence of iron in the dust inhaled by workers in iron foundries may account to some extent for Hamlin's findings and those of this survey. However this may be it is not perhaps unfair to claim that the results show the value of continued and constant medical supervision in foundries. The value of positive steps to control dust, whether toxic or not, is, however, unequivocal. Thus the fact that the use of silica parting powders was discontinued many years ago in these foundries and that relatively good control of dust has been instituted in the fettling department must have played their parts in improving the health of these workers. The first method is an illustration of the only certain means of controlling a toxic hazard, namely the substitution of a harmless for a noxious substance, while the second method is an example of the principle of controlling a noxious substance when it is not possible to substitute something harmless for it.

Nevertheless, complacency about the control of dust in the foundry is to be deplored, and it is reasonable to expect that the health of the foundry worker will be still further improved and the risk he runs due to the inhalation of noxious dust reduced as the result of the introduction of the further measures of dust control required by the Iron and Steel Foundries Regulations (Minister of Labour and National Service Statutory Instruments, 1953).

Summary

Recent studies on health and environmental conditions in iron foundries have been briefly reviewed.

A follow-up study has been made of 53 workers previously examined in 1943–44 and still working in the Butterley Foundries.

The incidence of respiratory disease amongst these workers has been low and evidence of progression in the *x*-ray films was absent in all save three of these men.

Naked-eye and histological studies of the lungs of a moulder who died as a result of an accident at work showed evidence of focal emphysema with pneumoconiosis.

The lungs of rats exposed to foundry dust in experiments showed little or no evidence of fibrosis. Radiographs of the rats' lungs showed distinct shadows, presumably due to iron oxide.

Some of the fine changes seen in the *x*-ray films of workers in these iron foundries may be partly due to the presence of radio-opaque dust and not necessarily to fibrosis.

Dust suppression and the use of silica-free parting powders are thought to have played a part in preserving the health of these foundry workers.

Positive steps to control the dust in all foundries are essential to maintain the health of the workers.

Thanks are due to Dr. Andrew Meiklejohn and to Dr. A. I. G. McLaughlin for reading the films and to the latter in addition for much helpful criticism and advice.

Part of the expenses of this work was met by a grant from the Research Fund of Sheffield University. The *x*-ray analysis of foundry dust was done for us by Dr. G. Nagelschmidt, of the Safety in Mines Research Establishment. The radiographs of the rat lungs were made by Dr. R. L. Gordon, also of that establishment. The photomicrographs were made by Mr. A. W. Collins, F.I.M.L.T. The dust estimations and temperature and ventilation assessments were carried out by Miss D. M. Pullon and Mrs. P. J. Hunt. Miss S. M. Smith and Mrs. I. J. Taylor were responsible for much of the routine work of the survey. Miss J. Andrews has given valuable help in the preparation of this article.

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AN INVESTIGATION OF WARTS PREVALENT AMONG WORKERS IN THE REDUCTION WORKS OF THE ALUMINIUM INDUSTRY

BY

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The reduction of alumina to produce the metal aluminium is associated with the manufacture of carbon electrodes for use in electric furnaces containing cryolite and alumina and heated by hydro-electric power. These electrodes, composed of anodes and cathodes, vary in character from blocks to paste, and are made from varying quantities of calcined coke and anthracite mixed with pitch obtained from the distillation of coke oven tar. Workers, therefore, come into contact with pitch dust in the carbon factory or fume in the furnace room to a degree in proportion to the process operated.

In recent years papers have been published stating, or presuming, that the skin of workers exposed to apparently similar hazards was likely to be affected by warts which were, in the opinion of some authors, probably pre-cancerous or even squamous epitheliomata (Fisher, 1953 ; Livingston, 1953). These opinions have naturally led to considerable alarm among both workers and management in this industry, and this investigation was instituted to determine as far as possible (1) whether the handling of pitch in the carbon factory or the exposure to fume in the furnace room is causing an increased incidence of warts among workers intimately exposed to them ; (2) whether duration of exposure or service increases the incidence ; (3) the effect of age ; (4) whether the warts found are cancerous or not.

An examination was made of the exposed skin surfaces of a large number of workers in two of the company's reduction works. The number examined was 553 out of 682 in one, and 545 out of 700 workers in the other. They comprised both males and females and the number missed was due to absence from work on examination days, for sickness, or on holiday. The skin surfaces examined were the face, neck, hands, and forearms, which were the parts most exposed to contact with fume and dust. The lesions noted were sessile and pedunculated papillomata, usually small, and all forms of cysts, boils, or other septic foci were disregarded, Barrier creams and goggles were worn by the majority of workers, while gloves were used by certain groups, *e.g.*, paste and certain furnace workers. As both factories are producing aluminium by similar processes and the workers are subjected to similar hazards, the findings for both works have been grouped together.

The employees in each factory were divided into the groups A, B, C, according to intimacy of exposure to the hazard : (A) Continuously in contact, (B) intermittently in contact, and (C) seldom or not at all.

The allocation of workers into these groups was determined not only by my own experience and knowledge of the hazards in the different jobs, but, after consulting with managers and personnel officers, who all had a very long experience of working conditions and who were unbiased as they were not informed as to the reason for my request. The groups were made up as follows :

Group A was composed of men working in jobs involving movement and replacement of anodes on furnaces, and those employed in the handling, breaking up and melting of pitch in the carbon factory.

Group B was composed of men and women employed in a variety of jobs in the furnace room and carbon factory, but not in such close contact with the hazard as those in Group A.

Group C comprised the office staff, power-house workers, and some transport workers and tradesmen, *e.g.*, joiners.

In addition to separating workers into varying

categories of hazard with the least degree of error, stability of job was also attained to the greatest possible extent. Each group was sharply divided regarding the type of job and wages earned so that change from one group to another seldom occurs, and then only on medical grounds or on leaving the industry.

Group D was a control group made up of 106 men and women of similar age distribution to the factory workers, living in the same locality. They were employed in the hotel industry and in the transport services, and they had never worked in the aluminium factory. Ten of those individuals who were garage hands had some contact with mineral oil, but none of the others had a history of contact with any recognized skin hazard.

Similar skin examinations were carried out in each individual, and a note taken of age and duration of service in his or her job. All the examinations were carried out by myself and were, therefore, not subject to varying interpretation of the conditions found.

Later representative warts were excised from each group and submitted to the Pathology Department of Glasgow Royal Infirmary for histological examination and report.

The results of the investigation are set out in Tables 1–5.

TABLE 1
FREQUENCY OF WARTS IN RELATION TO INTIMACY OF EXPOSURE IN FACTORY AND CONTROL GROUPS

Group	Number without Warts	Number with Warts	Total	Frequency (%)
A	70	101	171	59·06
B	204	227	431	52·66
C	193	303	496	61·09
Total	467	631	1,098	57·46
Control Group D	25	81	106	76·41

TABLE 2
AVERAGE NO. OF WARTS AND % FREQUENCY IN RELATION TO INTIMACY OF EXPOSURE

Site	Intimacy of Exposure Groups	No. of Warts												Total Personnel	No. with Warts	Total Warts	Average No. of Warts	% of Cases with Warts
		0	1	2	3	4	5	6	7	8	9	10	+10					
Face	A	158	9	1	2	0	0	1	0	0	0	0	0	171	13	23	1·77	7·6
	B	411	7	7	5	0	1	0	0	0	0	0	0	431	20	41	2·05	4·64
	C	412	53	19	8	3	0	1	0	0	0	0	0	496	84	133	1·583	18·9
	Total	981	69	27	15	3	1	2	0	0	0	0	0	1,098	117	197	1·65	10·65
	Group D	83	15	2	4	2	0	0	0	0	0	0	0	106	23	39	1·695	21·70
Neck	A	157	12	2	0	0	0	0	0	0	0	0	0	171	14	16	1·14	8·12
	B	399	18	9	3	2	0	0	0	0	0	0	0	431	32	53	1·67	7·42
	C	429	37	20	7	3	0	0	0	0	0	0	0	496	67	110	1·64	13·50
	Total	985	67	31	10	5	0	0	0	0	0	0	0	1,098	113	179	1·58	10·29
	Group D	89	11	5	1	0	0	0	0	0	0	0	0	106	17	24	1·411	16·04
Right hand	A	119	14	14	6	6	1	2	3	1	0	2	3	171	52	183	3·51	30·41
	B	295	35	28	34	10	7	7	2	2	0	4	4	431	136	448	3·37	31·55
	C	366	48	35	10	11	10	5	3	4	0	1	3	496	130	368	2·83	26·21
	Total	730	97	77	50	27	18	14	8	7	0	7	10	1,098	318	999	3·15	28·98
	Group D	58	23	11	7	4	1	1	0	0	0	0	1	106	48	104	2·177	45·28
Left hand	A	103	19	17	12	6	2	4	1	0	1	1	5	171	68	228	3·35	39·77
	B	295	32	34	26	11	6	8	4	7	1	2	5	431	136	468	3·44	31·55
	C	368	42	26	24	15	9	5	3	1	0	2	1	496	128	361	2·82	25·80
	Total	766	93	77	62	32	17	17	8	8	2	5	11	1,098	332	1,057	3·18	30·23
	Group D	79	11	8	2	3	2	0	0	0	0	0	1	106	27	66	2·444	25·47
Right forearm	A	137	14	10	4	1	1	1	1	0	0	0	2	171	34	90	2·64	19·89
	B	375	25	6	10	3	5	3	3	0	0	0	1	431	56	154	2·75	13·00
	C	407	48	17	14	6	0	1	1	1	0	0	1	496	89	180	2·02	17·94
	Total	919	87	33	28	10	6	5	5	1	0	0	4	1,098	179	424	2·37	16·30
	Group D	62	15	14	7	3	2	0	1	1	0	1	0	106	44	111	2·522	41·51
Left forearm	A	137	13	7	6	5	0	0	0	0	0	0	3	171	34	98	2·88	19·89
	B	361	25	15	12	8	4	2	2	0	0	0	2	431	70	191	2·72	16·24
	C	405	45	20	9	9	4	2	0	0	0	0	1	496	91	201	2·20	18·34
	Total	903	83	42	27	22	8	4	2	0	0	0	6	1,098	195	490	2·51	17·76
	Group D	75	15	8	5	1	1	0	0	1	0	0	0	106	31	63	2·032	29·24

The frequency of warts in group D workers is much higher than in any factory group, while there is no evidence of diminishing frequency from A to C Group (Table 1).

Table 2 shows the average number of warts and their frequency of occurrence on the face, neck, hands, and forearms among the factory and control groups.

The frequency for each site is usually higher in the control group except for the left hand, and the frequency in none of the factory groups diminishes regularly with intimacy of exposure except for the left hand. There is a higher frequency in Group A than in Groups B and C on the right and left forearms. There is, however, no regular diminution in frequency with decreasing intimacy of exposure. The highest rate is found in the face and neck in Group C among the factory workers.

The frequency in relation to both intimacy and duration of service is shown for the factory and control groups in Table 3. In Group B there is a regular increase in frequency with duration of service which is statistically significant. In Group A the highest rate occurs in the longest exposed group, but there is virtually no difference in the rates of those exposed respectively for none to five years and six to 15 years. In Group C and control group D the greatest frequency occurs in the middle age group. In the factory as a whole the increase with duration of service is regular but it could have happened by chance; moreover the rates for the controls at individual service lengths are consistently higher than for the factory groups, and as a whole the control rate is nearly half as high again as in the factory groups.

TABLE 3

FREQUENCY OF WARTS IN RELATION TO INTIMACY AND DURATION OF SERVICE IN FACTORY AND CONTROL GROUPS

Duration of Service in Years	% Frequency and Intimacy of Exposure				
	Factory Groups				Control Group D
	A	B	C	Total	
0– 5	55·55	46·80	58·29	52·88	73·23
6–15	55·00	57·75	65·11	61·28	88·88
16+	65·21	62·50	60·17	61·57	62·50
Total	56·72	52·66	61·09	56·19	76·41

Table 3A shows the frequency of warts for each site separately according to intimacy and duration of service. When all the factory workers together are considered a regular and significant increase of frequency of warts in relation to the length of service is found on both hands and left forearm but it is not found in any of the other sites.

TABLE 3A

FREQUENCY OF WARTS IN RELATION TO BOTH INTIMACY AND DURATION OF EXPOSURE FOR INDIVIDUAL SITES IN FACTORY AND CONTROL GROUPS

Duration of Service in Years	% Frequency and Intimacy of Exposure				
	Factory Groups				Control Group
	A	B	C	Total	
Face					
0– 5	6·48	4·25	17·06	9·56	21·12
6–15	5·00	5·17	15·69	10·67	22·22
16+	17·39	5·00	20·79	14·21	25·00
Total	7·60	4·64	17·35	10·77	21·70
Neck					
0– 5	8·33	8·17	14·69	10·65	22·53
6–15	10·00	6·89	16·27	12·19	03·70
16+	4·35	6·33	7·08	6·48	00·00
Total	8·18	7·42	13·50	10·20	16·04
Right hand					
0– 5	25·00	24·25	23·69	24·18	45·06
6–15	40·00	36·20	27·90	32·31	44·44
16+	39·13	46·25	28·31	36·11	50·00
Total	30·40	31·55	26·21	28·96	45·30
Left hand					
0– 5	35·18	26·80	24·17	27·43	22·53
6–15	47·50	34·48	23·25	30·18	33·33
16+	47·82	41·25	32·74	37·50	25·00
Total	39·76	31·55	25·80	30·24	25·50
Right forearm					
0– 5	14·81	6·38	14·69	11·19	38·03
6–15	30·00	18·10	25·00	23·17	51·85
16+	26·08	25·00	13·27	18·98	37·50
Total	19·88	12·99	17·94	16·30	41·50
Left forearm					
0– 5	15·74	8·93	15·16	12·63	22·53
6–15	25·00	22·41	22·09	22·56	44·44
16+	30·43	28·75	18·58	23·61	37·50
Total	19·88	16·24	18·34	17·75	29·24

A similar regular increase in frequency with duration occurs in Group B in the right and left hand and right and left forearm. In none of Groups A or C in any site does such as increase occur except that which could happen by chance, while in the neck an opposite association is found.

In the control group the only regular increase is found in the face and is not statistically significant. In all other sites no regular association is found with length of service, while a much higher frequency rate is found in all sites than in the factory groups except in the left hand.

Table 4 shows that there is a regular increase in frequency of warts with advancing age for all factory workers and in the control group, whereas for intimacy a similar association occurs only in Group B. In the age groups a diminishing frequency of warts from Groups A to C occurs only in the highest age group.

It is noted also that the frequency rates in Group D are much higher than in any factory group.

TABLE 4

FREQUENCY OF WARTS AND INTIMACY OF EXPOSURE IN RELATION TO AGE IN FACTORY AND CONTROL GROUPS

Age Groups	Frequency of Warts and Intimacy of Exposure				
	Factory Groups				Control Group D
	A	B	C	Total	
15–35	57·14	48·26	58·71	54·48	73·75
36–55	56·94	55·91	70·37	61·66	83·33
56+	100·00	80·00	64·15	71·05	100·00

Since in Group B the association with age was the most significant, and the correlation of warts with length of service for hands and forearms the most regular, it is necessary to see if this association is related to advancing age or to duration of service.

TABLE 5

FREQUENCY OF WARTS IN GROUP B ACCORDING TO AGE AND DURATION OF SERVICE

Duration of Service in Years	Age Groups		
	15–35	36–55	56+
0– 5	43·67	45·57	66·66
6–15	39·13	64·00	64·28
16+	50·00	59·67	64·28
Total	43·17	56·01	64·51

Table 5 shows that in each group according to duration of service a regular increase in wart frequency is found with advancing age, whereas in each age group no regular increase in wart frequency is found with increasing duration of service.

Discussion

The investigation involves contrasts between the control and works groups, and in the works groups an assessment of the association of wart incidence, if any, with intimacy and duration of exposure as well as age to the suspected agent. Owing to the number of workers examined who were representative of various skin types, it is assumed that no single type of individual preponderates, and therefore no assessment of individual type is included. If working conditions, therefore, have an effect on incidence of warts the tabulations should satisfy the following conditions : (1) A diminishing frequency of warts from Groups A to C and a lower frequency in control Group D ; (2) an increasing frequency with length of service ; (3) an increasing frequency with age greater than any normal rise with age.

The contrast between the control and works groups shows a decidedly higher incidence in most sites in the control series than in the works personnel as a whole, or with those workers most intimately and constantly exposed to the suspected agent.

A contrast of the incidence in the three groups of intimacy does not show any relationship, and no tendency for those most intimately exposed to show most warts on any site.

As regards duration of service, most of the groups show irregular and statistically insignificant relationships except in those tabulated. These all show an increase in frequency of warts with duration of service. On the other hand, exactly the opposite relationship seems to obtain in respect of warts on the neck in the intimacy groups as well as in the total. A large proportion of the other sites and many varying groups show no regular increase in frequency for either duration or intimacy of exposure.

In control Group D an increase in frequency with length of time in the job is seen in the face only, and all other sites show an irregular association with generally much higher frequency rates than in corresponding groups in the factories.

Advancing age does show an increase in frequency of warts in Group B and for the factory group totals. The control group, however, also shows a significant association with advancing age. Except for the oldest age group there is no evidence of increasing frequency of warts with intimacy of contact.

The association with the length of time on the job found in the hands and forearms in Group B is in all probability due to the correlation with advancing age rather than to duration of service.

A wart each was excised from six persons representative of the different groups, and of varying lengths of service, and these were sent to Dr. A. R. Currie, of the Department of Pathology at Glasgow Royal Infirmary, for histological examination, as follows :

Specimen No.	Name	Duration of Employment (years)	Type of Work	Group
1	J.S.	41	Carbon factory	A
2	M.G.	11	,, ,,	A
3	C.G.	1	Furnace room	B
4	R.B.	23	Clerk	C
5	R.T.	15	Civil engineer	C
6	J.M.	6	Garage hand	D

Dr. Currie was informed beforehand that some of the specimens were excised from individuals working with pitch, but he was unaware of the groups, or of which one was the control. He reported as follows :

" The lesions are all of a similar nature. They are simple papillomatous tumours in which there is hyperplasia of the prickle cell layer but little deepening or broadening of the interpapillary processes.

Mitotic figures are present in two of the tumours but otherwise they present little evidence of activity. There is little or no melanin pigment in the basal cell layer of the lesions, and there is only a scanty lymphocytic infiltration around the blood vessels in the superficial corium.

"It is not possible to indicate from the histology alone whether the lesions are of an infective nature or due to an exposure to pitch."

The mitotic figures mentioned were present in specimens Nos. 2 and 3, and in subsequent discussion Dr. Currie stated that they represented evidence of a more rapid growth than in the other warts but of a simple nature only, while it was interesting to note also that it occurred in the men with the shortest duration of service. The most important finding appears to be that the warts examined from Groups C and D presented similar appearances to those in the other groups, and that there is no histological evidence of malignancy in any group.

Conclusions

Warts prevalent among workers in the reduction works of this industry are, on the sites selected in this enquiry, very frequently found in the general population. We find actually that their frequency is greater in a control group than in the population of the works, where the influence of a carcinogen is suspected. Among the workers there is no strong or regular evidence of association or length of exposure to the presumed agent. Duration of service shows in the instances already mentioned a difference in frequency suggestive of increase with greater length of service, but on other occasions either a reverse association, or no definite relationship at all is found. The influence of age on wart frequency is similar in both the factory and control personnel.

The histological examination shows that the warts from the works groups and the control group are simple papillomata, and that it is not possible microscopically to indicate that these warts are due to pitch, and that in no case was any evidence suggestive of malignancy detected.

The collective evidence of this investigation is consistent with the view that the skin warts observed in the aluminium workers are not produced by an industrial agent.

Summary

An examination of the exposed skin surfaces of 1,098 out of 1,382 workers in the Aluminium Company's reduction works was carried out, and the number and distribution of warts found are tabulated and discussed.

From the evidence it would appear that the degree of exposure to a presumed carcinogen among workers operating the various processes in the aluminium works is not necessarily productive of cancerous warts.

I wish to thank Dr. A. R. Currie for his kindness in supplying the histological report.

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THE JULY (1954) ISSUE

The July (1954) issue contains the following papers :—

Some Toxic Properties of Dimethylnitrosamine. By J. M. Barnes and P. N. Magee.
A Report on 235 Cases of Erysipeloid in Aberdeen. By D. M. Proctor and I. M. Richardson.
Raynaud's Phenomenon in Workers with Vibratory Tools. By R. P. Jepson.
The Treatment of Complicated Pneumoconiosis with Isoniazid. By W. E. Miall, P. D. Oldham, and A. L. Cochrane.
Silica and Collagen in the Lungs of Silicotic Rats Treated with Cortisone. By B. D. Stacy and E. J. King.
The Development of Compensation for Occupational Diseases of the Lungs in Great Britain. By Andrew Meiklejohn.
Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. Part II : Further Consideration of the Role of Aniline and the Manufacture of Auramine and Magenta (Fuchsine) as Possible Causative Agents. By R. A. M. Case and Joan T. Pearson.
Thermal Conditions in Warships Refitting at H.M. Naval Base, Singapore. By G. Southwell-Sander.
Miscellanea :
Some Personal Observations on Industrial Health in the United States of America. By Bryan Harvey.
Second Conference of the British Occupational Hygiene Society. By R. J. Sherwood.
Obituary :
Edward Provan Cathcart.
Raymond Hussey.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

MISCELLANEA

Some Recent Inquiries and Current Problems in the Social Organization of Industry

D. H. ALLCORN

From the Department of Social Anthropology, University of Manchester

In industry changes in the methods and organization of work as a rule do not provide all the benefits expected of them. Some have unanticipated social and psychological repercussions, and thus the advantages of technological changes are frequently offset by social forces which the changes themselves have introduced. Although these forces are not always well understood, some encouraging progress has been made recently in sociology.

Two main types of inquiry contribute to our present knowledge of social process and structure. First, there is the kind of inquiry which Elton Mayo (1949) and his colleagues (especially Roethlisberger and Dickson, 1939; Roethlisberger, 1942) carried out at the Hawthorne Plant of Western Electric and addressed to the most readily observable forms of social relationship. Secondly, there are studies which seek to use a series of observed events as indices of processes which, initially at least, cannot be directly observed. A good example of the latter is the Acton Society Trust's recent publication *Size and Morale*.*

This report, which is "essentially a sample of work in progress" draws upon information from the coal industry, from a large industrial concern controlling nearly 100 separate undertakings, and from a commercial concern with 230 retail stores. It deals mainly with the associations to be found between rates of attendance and absence, and the size of the local undertaking.

Despite the difficulties of getting comparable information from different industries, the Acton Society Trust has secured three sets of data which are sufficiently alike to permit of certain broad comparisons. The most important statistical findings are summarized in the Table. In all three cases, attendance at work is inversely related to the size of the local undertaking. In the coal industry, correlations between various measures of attendance and size are of the order of 0·60, in the industrial concern 0·40, and in the commercial concern around 0·25.

In one area of the National Coal Board where the average number employed in the collieries was 1,600, 21,000 miners won as much coal as did 25,000 miners who worked in similar geological conditions in a neighbouring area, where the average number employed in the collieries was 2,500. In the East Midland coalfield it is estimated from the association between size and output that if the average size of colliery was doubled productivity would decline by about two-fifths.

TABLE
ATTENDANCE AT WORK AND SIZE OF LOCAL UNDERTAKING

Index of Attendance	Industry	Unit and Period of Observation	Correlation Coefficient
Proportion of bonus shifts worked	Coal-mining	18 pits for 3 months	−0·67
Absence rates	,,	25 wage districts for 12 months	+0·60
All absences of hourly paid men	An industrial concern	91 factories for 12 months	+0·45
All absences of hourly paid men due to sickness	,,	,,	+0·41
Absences other than those due to certified sickness	,,	,,	+0·33
All absences	A commercial concern	230 retail stores for 12 months	+0·24

In the coal-mining industry of Britain as a whole the accident rate increases steadily with the size of the pit; from 63·5 per 100,000 manshifts in pits employing fewer than 50 men, to 166·6 in those employing more than 3,000. Among the factories of the industrial concern, the larger ones tended to have higher accident rates, and the duration of absence following accidents in them was longer.

Most of the accidents which occur at work are not directly due to the technical operations carried out. In the factories studied, only one-twentieth of the accidents were directly due to technical mishaps. In the collieries, it was the accidents that occurred on the surface and those due to stumbling which were most likely to increase with the size of the colliery, not those due to falls at the coal face. A detailed examination at one colliery of the daily variations in absences, and of the explanation given for these absences, showed that on Mondays, the day of the week on which most men were away from work, there was an increase in each category of explanation. Moreover, the relative increase in each category was similar. On Mondays there were more men who explained their absence as due to oversleeping than on other days of the week; there were also more men whose

* *Size and Morale: A Preliminary Study of Attendance at Work in Large and Small Units.* Acton Society Trust (1953). Pp. 44. Price 3*s*. 6*d*.

absence was due to certified sickness and to having had accidents.

By the accumulation of such instances, a strong case is built up for treating the rates of absences, accidents, and the like, as the outward and visible signs of underlying processes connected with the structure and functioning of social groups.

These findings, and the results of similar inquiries, can be examined in relation to four sets of major variables: (1) the formal structure of the local undertaking, and the larger concern of which it is a part; (2) the composition of the labour force; (3) the informal social organization among workers and within management; and (4) the nature of the local community in which the undertaking is situated. These major variables are all related one to another, and each of them consists of several components which are also interrelated.

The Formal Structure of the Undertaking

An undertaking which has grown into a larger organization has usually developed a complex internal structure. Whatever the actual methods of production used, they necessitate certain social relationships between workers and management, and also among the workers and within the management. In larger undertakings, actual work on production and the organization of production inevitably become sharply set apart from one another. The relations between those engaged on different tasks become more specific and impersonal. Communications have to be more formal and selective, and concentrated in fewer channels. Greater complexity of the methods of production and the consequent specialization within management create pressures towards greater departmental autonomy. The purpose of these departments, originally conceived as means for realizing the ends of the whole organization, become ends in themselves to be realized even at the expense of other departments, and thus eventually of the larger organization. The situation is a familiar one in the National Health Service and the social services generally.

The analysis by Trist and Bamforth (1951) of the "long-wall" method of coal-mining provides an excellent example of this process among workers actually engaged on production. The method, the one most commonly used in Britain, divides the work up into 24-hour cycles of production, each comprising three shifts. A new cycle can begin only when the previous one has been fully completed. Similarly, each shift can accomplish its tasks successfully only if the previous shift finished off its work properly. The different tasks to be done on each shift are related far more directly to some of those carried out by the preceding and succeeding shifts than to other tasks carried out on the same shift. For the most part, even those men who do the same work on the same shift are not organized in teams but remain aggregates of individuals working in parallel. In short, a method of working which necessitates highly coördinated tasks at the same time separates, physically and socially, the very workers who need to cooperate, for it is the social relations which arise where people work together, and the social controls inhering in these relations, which most effectively regulate the performance of common tasks (Homans, 1951).

It is possible, then, that underneath the social difficulties there is a conflict within the social organization of industry which is both fundamental and inevitable. The tendency towards increased specialization and minute sub-divisions of labour separates physically and socially the workers engaged on various tasks while increasing the interdependence of these tasks. The methods which are designed to simplify and standardize parts of an operation increase the complexity of the whole. The very arrangements which create the need for closer cooperation hamper and even prevent the development and maintenance of necessary social relationships.

Similar problems arise in supervision. Much of the work of actually organizing production and setting the pace, originally carried out by foremen, has passed to production engineers and rate-setting departments. The tasks of supervisors are becoming increasingly limited to those of routine supervision and of keeping production up to the levels specified by other departments—to "police-work" in fact. Such procedures may be satisfactory up to a point. The Acton Society Trust's report establishes the fact that in most of the National Coal Board's areas an increase in the proportion of supervisors to other workers was attended by a decline in the absence rates. In the commercial concern, where the span of control (that is, the number of workers per supervisor) was much narrower than in mining, there was no correlation between absence-rates and the proportion of supervisors to staff. The absence-rates of those N.C.B. areas which already had a comparatively narrow span of supervisory control did not decline when still more supervisors were employed. Moreover, measures to reduce the span of control at the lowest level of supervision introduce new difficulties. An increase in the number of supervisors at this level entails either an increase in the span of control at the next level, or an increase in the number of levels within the executive structure. A strike of the first-line supervisors at a large Yorkshire colliery suggests that this familiar dilemma of industrial administration is already having repercussions.

Composition of the Labour Force

Comparisons of absence-rates and labour turnover in different industries must take into account gross variations in the composition of the labour force. Generally speaking, skilled workers change their jobs less frequently than the semi-skilled and unskilled, men less often than women, older workers and those who have worked for longer periods in an undertaking less than younger workers and those who have worked for shorter periods (Social Survey SS 134, 1945–49; Long, 1951). Absences from work follow much the same trends except that the oldest workers are more often away than the younger and the middle-aged (Behrend, 1951).

The mining industry employs men almost exclusively, and has a comparatively stable labour force. To some extent this counteracts the disruptive tendencies of the

long-wall method of mining, and enables some social relations with workmates to persist. Thus, what happens inside an undertaking may be more significant than what goes on outside. The commercial concern employs women for the most part and will have a constantly changing labour force. In this kind of situation workers are more likely to be affected by what happens outside the undertaking than by what happens inside it. Such factors partly account for some of the apparent discrepancies in the Trust's findings. The correlation of the absence-rate with size of undertaking was highest for the collieries and lowest for the chain stores ; the correlation of absence-rates with the size of the town in which the store was located exceeded that between absence-rates and the size of the store itself. The corresponding correlation between size of undertaking and absence-rates was higher among those workers of the industrial concern who had staff grading and who, generally speaking, would be the older employees and those with longer service, than among those who did not have staff grading. Demographic considerations, then, can afford valuable clues to the internal structure of groups.

Informal Social Organization

It is now generally accepted that social groupings develop among people working together even though there may be little or no functional connexion between the tasks on which they are engaged (Moore, 1951). The persistence and solidarity of these groups are much affected by the formal structure of the undertaking, and such features of its labour force as the amount of labour turnover. In the more stable of such groupings, standards of expected behaviour and means of controlling departures from them become firmly established. Such norms may regulate not only output but the extent to which other rules laid down by the management are actually observed. It should not be supposed that the norms of informal groups always run counter to the aims of the management. In Britain, for instance, the " normal " working of the railways depends upon disregarding some of the official regulations ; the entire system can be paralysed if the railwaymen decide to observe regulations meticulously and " work to rule ".

Though sociologists have not yet produced satisfactory general propositions covering relations between formal structure and informal organization in industry, the available evidence is fairly consistent. It suggests that the informal social organization is more effective when the size and stability of the working group defined by the formal structure enable all the workers to be included in a single informal group, however much this may be further divided into sub-groups and cliques (Miller and Form, 1951). The Trust was able to show that pits working several seams simultaneously returned absence-rates and accident-rates which were significantly lower than those for other pits in the same area employing a similar number of men but working only a single seam. This is in line with the earlier findings of Marriott (1949) and of Hewitt and Parfit (1953). The former showed that in two engineering works output was inversely related to the size of the group engaged upon a particular set of tasks. The latter studied a hosiery factory which employed chiefly women, who worked in rooms of different sizes. Although those who worked side by side in the same room were not organized as a team or paid on this basis, absences for reasons other than certified sickness from the larger rooms were in significant excess of absences from the smaller rooms. Clearly, informal social organization must be considered as well as the formal structure of the undertaking.

The Nature of the Local Community

In the past, the nature and needs of local undertakings have determined the sites, shape, and size of many industrial towns and villages in Britain. Often they owned the houses in them and the very ground on which they stood. The local community may quite literally still live in the shadows of the undertaking for which it provides the labour force. In these circumstances it is inevitable that the social forces operating within the undertaking and those which operate outside it will markedly affect each other. Thus differences in the balance between the social forces inside and those outside the undertaking may partly explain observed differences in the correlations between various measures of absence. It is certainly pertinent that in the coal industry, where local undertaking and local community are still most closely connected, all measures of absence are correlated with one another and with the size of the undertaking ; in the industrial concern there was no correlation between absence without leave and size. Many miners live among the men with whom they work ; social relations effective within the pit are often maintained outside it, and vice versa. Here, very possibly, the informal group regulates not only behaviour at work but whether or not men come to work at all. Among those who work in factories, offices, and shops, there is far less overlap between what happens at work and life outside. Especially in larger towns and cities people who work together are far less likely to mix with one another in their leisure time. It has already been pointed out that in the commercial concern, absence was, if anything, more closely associated with the size of the town than with the size of the store.

The study of the relations between the internal structure of the undertakings and the communities in which they are set poses many difficult problems of research method. Nevertheless, an examination of the other issues already touched upon eventually leads back to this problem, perhaps the most crucial in social inquiry today.

From time to time, the interests of distinct and separate disciplines converge. Absences from work due to accidents, certified sickness, and other causes, their incidence, and factors related to the ways in which they vary are of importance not only to economists, psychologists, and sociologists, but also to doctors, especially those practising industrial and social medicine. At the same time, procedures for studying these matters are not highly developed. Indeed, further research, so far from contributing to present practice, will probably begin by emphasizing its deficiencies. This is unlikely to

cause alarm in medicine where advances in knowledge have frequently begun in this way.

Research of this type will lead to a general realization that behaviour at work is social behaviour and work itself a social activity. Exhortations about how people should behave addressed to people conceived of either as isolated individuals or as an undifferentiated mass are beside the point. People live and work in social groups of one kind or another and the individual rarely creates the norms of the groups to which he belongs. But the problems involved in studying these complex systems of social relations are immense, and the procedures for investigating them but little developed. It is a peculiar excellence of *Size and Morale* that it directs attention to issues which can be profitably studied with techniques already available.

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Third Conference of the British Occupational Hygiene Society

The Society's third conference has been arranged for Monday, November 1, 1954, starting at 11 a.m. and will be held at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1. (by kind permission of the Dean). The conference will be devoted to a discussion of radiation hazards in industry. The conference is open to non-members (on payment of the conference fee) as well as to members of the Society.

The Chair will be occupied by the President, Professor E. J. King, Professor of Chemical Pathology at the Postgraduate Medical School, University of London.

Four papers will be presented. There will be a short discussion after each paper. Abstracts of the papers will be sent to all those who have notified the Hon. Treasurer of their intention to be present.

The conference will be reported in the January, 1955, issue of the *British Journal of Industrial Medicine*.

Programme

11 a.m. Opening of the Conference by the President.

11.5 a.m. **The Health of Workers Exposed to Ionizing Radiation**, by A. S. McLean, M.B., Ch.B., D.I.H., Principal Medical Officer, Department of Atomic Energy.

12.5 p.m. **Radiation Safety in the Industrial Group of the Department of Atomic Energy**, by D. R. R. Fair, O.B.E., B.Sc., A.Inst.P., Head of the Health Physics Division, Department of Atomic Energy, Windscale Works, Sellafield.

1.5 p.m. Luncheon interval.

2.30 p.m. **Protection against X rays and Gamma rays in the Industrial Field**, by W. Binks, M.Sc., F.Inst.P., Radiological Protection Service, Ministry of Health and Medical Research Council.

3.30 p.m. **Safety Criteria in Atomic Energy**, by F. R. Farmer, B.A., Assistant Director (Production), Department of Atomic Energy, Industrial Group Headquarters, Risley.

4.30 p.m. Adjournment for tea.

The Hon. Secretary is Peter C. G. Isaac, Public Health Engineering Laboratory, King's College, Newcastle-upon-Tyne.

Occupational Mortality

The Registrar General's reports on occupational mortality are laborious and time-consuming undertakings and usually appear several years after the census of populations on which they are based has been taken. The last report from the 1931 census was published in 1938. The calculation of death rates in relation to the 1951 census is being made for a five-year period (1949 to 1953) instead of the usual three years, and the report cannot be expected before 1958.

Using the death rates in 1950 the Registrar General for England and Wales (1954) has calculated comparative mortality rates in the main social classes and in a few large occupational groups. While these figures will not be as reliable as those in the full reports, they go some way to fill the gap in occupational mortality data during the past 20 years. Those with experience of certain occupations or diseases have been invited to contribute commentaries on the data contained in this latest report. The first two contributions follow.

Cancer of the Respiratory Tract

RICHARD DOLL

In the 20 years that have elapsed between the last two censuses the mortality from lung cancer has increased sixfold and it is, therefore, of particular interest to see whether there has been any change in the social distribution of the disease to accord with the distribution of any of the factors which may be responsible for the increase. In the period 1930–32 the mortality from lung cancer varied little from one social class to another and there was no indication of a gradient in either direction with descent in the social scale. It appears now that among men aged 20–64 the disease may be less common in the wealthiest classes (standardized mortality ratio for Class I, 80, for Class V, 116). This tendency, however, is not evident for older men or for women of either age group.

None of the occupational groups specified by the Registrar General in the present limited statistics shows a grossly high mortality—the highest being men in the Armed Forces aged 20–64 with a standardized mortality ratio of 150, but, as previously, consistently low mortalities at all ages are recorded for farmers, agricultural workers, and mineworkers, and for the wives of men in all three groups. When these special groups are removed the upward gradient in mortality with descent in the social scale for men aged 20–64 years becomes much more definite :

	S.M.R. in Social Class				
	I	II	III	IV	V
Men aged 20–64 years ..	80	79	108	89	116
Men aged 20–64 years, less farmers, agricultural workers, and mineworkers	80	85	109	107	116

Were a similar gradient found among older men and among married women it might be possible to attribute this finding to an effect of atmospheric pollution, since it is not unreasonable to believe that more of the men in the poorer social classes tend to live in the more polluted areas. The facts are, however, otherwise, and indeed the highest standardized mortality ratio among married women is found in social class I.

	S.M.R. (or Proportionate Mortality Ratio) for Persons over 65 in Social Class				
	I	II	III	IV	V
Men aged 65 years and above*	108	102	109	106	118
Married women aged 20–64 years†	*120*‡	99	106	116	91
Married women aged 65 years and above†	*176*	*110*	101	*111*	*103*

*Less farmers, agricultural workers, and mineworkers.
†Less wives of farmers, agricultural workers, and mineworkers.
‡Ratios in italics based on fewer than 50 deaths.

Differences in cigarette consumption could account for the high mortality among the wealthier women who may well have begun smoking a decade or more earlier than the average, but whether they can account for the increasing mortality with descent in the social scale among men under 65 years and for the low mortality among farmers, agricultural workers, mineworkers, and their wives is unknown. Such a factor would, one suspects, accord well with the high mortality from lung cancer which occurred in the Armed Forces.

The consistent findings of a low mortality for mineworkers (S.M.R. for mineworkers aged 20–64 years in Class III, 92 ; in Class IV, 55. Proportionate ratio aged 65 years + in Class III, 61 ; in Class IV, *56*) once again confirms the lack of association between lung cancer and exposure to dust *per se*.

Cancer of the larynx has, in the past, provided a good example of a type of cancer which was closely dependent on social conditions. The increasing gradient with descent in the social scale revealed in 1921–23 is, however, now no longer apparent. This may, perhaps, reflect social changes in the consumption of alcohol. The present report does not give figures for workers in the alcoholic trades and it is not certain that the previously observed association with alcohol persists.

Transport Workers

L. G. NORMAN

The 1951 Supplement differs in a number of respects from those previously published. There are marginal differences due to revisions in the Classification of

*Registrar General's Decennial Supplement England and Wales (1951). *Occupational Mortality, Part* 1. H.M. Stationery Office, London.

Occupations and in the International Classification of Causes of Death, but these are of only minor importance. For the first time, however, transport workers are separated as a special social sub-group, IIIb. This sub-group of social class III includes a very mixed selection of transport workers such as locomotive engine drivers and motormen, guards, signalmen, shunters ; haulage contractors and managers, inspectors and foremen ; drivers of trams, trolleybuses, buses and goods vehicles ; ship engineering officers and electricians, petty officers, seamen and radio officers, pursers and domestic staff ; aircrew, aerodrome technical staff, airport traffic staff and other air transport workers. Excluded are railway officials, locomotive firemen and running shed workers, ticket collectors, porters and other railway workers ; bus and tramway managers and superintendents, coach hire proprietors and managers, drivers of horse-drawn vehicles, lorry drivers' mates and van guards, bus and tram conductors, horse foremen and grooms, garage managers and other road transport workers ; shipping managers and agents, harbour, dock, and canal officials, wharfingers and stevedores, navigating officers, firemen and trimmers, bargemen, dock labourers, and other water transport workers ; messengers, telephone operators, postmen. The majority of those excluded are in social class IV ; it is rather surprising that bus drivers are in social class III while driving instructors and conductors are in social class IV, but, as is clearly described in the Supplement, the classification is not based on economic considerations but on " general standing within the community ". Surely a somewhat arbitrary and even dangerous classification to adopt ! It is clear that the question, " What is a transport worker ?" needs close examination before any deductions are made from the statistics provided.

Table IB of the Supplement shows that there were 726,000 occupied and retired men classified in the very varied occupations comprising social sub-class IIIB (transport workers) of the 1951 Supplement ; they had 616,100 wives. The mortality of such a large group is likely to follow closely the national mortality and an examination of the figures reveals that this is so. As a social picture of a mixed body of road, rail, water, and air transport workers, the Supplement gives the mortality of occupied and retired men in these occupations by 36 different causes, in age-groups 20–64 and proportionate rates for those aged 65 and over ; similar figures for their wives ; neonatal and infant mortality when the father is in these occupations, and the stillbirth rate. The standardized mortality ratio (S.M.R.) of male transport workers at all ages is 104 ; of their wives 102 ; the infant mortality is 105% of all classes, and stillbirths 98% of all classes. For the reason given above all these figures approximate fairly closely to the national average. Mortality statistics for large occupational groups may conceal a high mortality in a small part of the group, the smaller the part the greater the mortality which may be concealed. While this limitation should be borne in mind, there is no reason to suppose that a high mortality exists in any subdivision of the occupational group of transport workers.

As regards the 36 individual causes of death, as is not unexpected, road vehicle accidents have an S.M.R. of 127, an excess which does not occur with the wives. There are no other particularly high or low ratios, except—surprisingly—for malignant neoplasms of kidney, bladder, and other urinary organs, with an S.M.R. of 172 (standard error 19·3) for men aged 20–64 ; this excess is repeated for men aged 65 and over, with a death rate per 10,000 of 116 as against 85 for social class III as a whole. This excess is not apparently repeated for the wives in both age groups, but the number of deaths is small. It would be interesting to know whether this excess occurred at any one site or in any particular occupational group. Perhaps the warning given in the introduction to the Supplement applies here, however, and because sample figures of the census are used and because the figures of deaths are based on only one year's returns, the scope of possible distortions in the results may be larger than in previous more comprehensive studies.

A comparison with the Occupational Mortality Supplement based on the 1931 census is unfortunately not possible, as the transport workers are subdivided into different and more detailed occupational groups in the earlier report. It is to be hoped that comparable tables will be included when the final Supplement based on the 1951 census is published.

There is a great deal of valuable material for study in the Supplement based on the 1% samples of the 1951 census, and the Registrar General and his staff are to be congratulated on their initiative in producing this preliminary publication of occupational mortality statistics.

BOOK REVIEWS

The Later Working Life in the Building Industry. A Study of 320 Ageing Maintenance Workers. By F. Le Gros Clark. (Pp. 21. no charge.) London : Nuffield Foundation. 1954.

The author was given access to the " dead files " of the maintenance section of London County Council's Housing Department ; from these he extracted the records of 320 men " whose careers (in that Department) were more or less traceable from the age of 60 onwards ". The group comprised 100 painters, 100 other tradesmen, and 120 labourers. The ages at which these men left the L.C.C. maintenance section were used to estimate wastage rates from age 60 onwards and from evidence contained in the records wastage was attributed to such factors as ill-health.

In his background information the author states that the L.C.C. was a tolerant authority which in the post-war years " was not at all rigid in its policy of discharge of men who reached the pensionable age ". He emphasizes that the men were all on maintenance jobs in which the chance of retention for an older worker was probably higher than on the constructional side of the building industry.

As to his method of study, Mr. Le Gros Clark unfortunately fails to describe fully the nature of the records from which he has derived his data. The procedure in use when a man leaves is not described and it is therefore doubtful how much weight can be attached to the recorded reasons for leaving. The apparently common occurrence of such expressions as " age " in the records suggests that the precise circumstances of leaving were often either not examined or not noted by those responsible for completing the records, presumably because they did not consider it relevant to do so. Hogben and Cross (1954) have recently discussed this kind of situation and stressed that unless records call for information on precise points, the value of what information they do contain must be in doubt.

In all such studies as this there is inevitable difficulty in establishing comparability between men reaching the same age at different points in time. Mr. Le Gros Clark has taken age 60 as the starting point of his 320 men but he does not give the actual year dates of their leaving nor does he do more than refer broadly to their length of service with London County Council. Even in the short period of years over which the men presumably left, employer attitudes to older men might have changed and it is well known that length of service is taken into account when making decisions about retirement.

With these possible sources of error in mind some comment may now be made on the findings. The author emphasizes that the smallness of his sample makes conclusions tentative. He postulates from the data that, if the 320 men are regarded as coming into view at age 60, between 70 and 75% " could be expected to reach the age of 66 in a reasonable state of working efficiency " (with reference to the particular occupations under study) ; at age 70 about 30% of the original 320 men were still in the labour force. The total wastage rate was about the same in tradesmen and labourers. In the discussion of wastage rates at different ages the report stresses the fact that those who are still at work over 70 are quite exceptional physically. The fascination of extremes has not misled this author.

In the report frequent reference is made to the numbers of men leaving on account of " age ". This is a most unsatisfying reason for retirement unless it is accompanied by some pointer to the particular effects of ageing which have reduced mental and physical efficiency. If we are to seek the truth about such an important social and personal event as retiring, precise information about reasons and circumstances should replace vague expressions like " age ". What we want are measures of age in terms of ability.

The contribution of ill-health to wastage was cautiously computed by the author from statements on the records. It was evident that disability took a heavy toll in the late 60s, there being few light jobs available in the industry. Perhaps the most interesting and important finding was that 17% of the 320 men left within one to three months of their return to work after a spell of sickness absence. This kind of event has been observed by other investigators and merits intensive study. Mr. Le Gros Clark suggests that " rehabilitation " might reduce this proportion but he does not indicate what forms of rehabilitation he has in mind.

Despite the limitations imposed on the data by uncertainties about the records on which the study is based, this report has real value in that it replaces impressions by numerical information. Breaking new ground is usually difficult ; we should be grateful to the author for laying bare promising points for further investigation, and we can look forward to reports on the future studies which he is to make for the Nuffield Foundation.

I. M. RICHARDSON

Symposium on Fatigue. Edited by W. F. Floyd and A. T. Welford. Vol. I. (Pp. viii + 196 ; 47 plates. 24*s*.) London : H. K. Lewis. 1953.

This volume consists of 20 papers which are most of those read at a meeting of the Ergonomics Research Society in March, 1952. The society numbers amongst

its members research workers in the fields of several biological and mechanical sciences and it was the former who contributed to the symposium, which was the second held by the society.

Half of the papers are by psychologists and the volume properly opens with a challenging definition of fatigue by Sir Frederic Bartlett :

> " Fatigue is a term used to cover all those determinable changes in the expression of an activity which can be traced to the continuing exercise of that activity under its normal operational conditions, and which can be shown to lead, either immediately or after delay, to deterioration in the expression of that activity, or, more simply, to results within the activity that are not wanted."

Although no other contributor attempts to define the term, almost all of them in fact use it in a sense compatible with this definition. It is this clarity of view and the penetrating exposition of psychological criteria of fatigue which follow from it that make the subsequent chapters seem relatively pedestrian. In fact they are not, but are confined mainly to descriptions of experimental anatomical, physiological, and psychological researches for the most part new, and never before so accessibly presented.

The diversity of disciplines is reflected in the wide range of topics covered, from tropical fatigue as a result of months of residence in tropical areas, to detailed changes in performance resulting from only one minute of psychologically exacting work. Because of the relative ease of objective measurement, it is clear that the physiologists are considerably in advance of the psychologists in this field. In particular many psychologists in this country will for the first time make the acquaintance of the work of E. H. Christensen, whose factory studies are models of applied physiology of interest to all concerned with problems of fatigue in industry. It is evident from this volume that physiologists have passed the stage of the development of techniques, and, when the activity is such that their techniques are applicable, we may expect a rapidly growing body of knowledge aimed at the alleviation of physical fatigue. The many different angles from which " psychological " fatigue is discussed indicate all too clearly that psychologists are still groping for something to measure and for something with which to measure.

Yet the value of this book is that it does bring together a variety of approaches and abundant and fascinating experimental data, and a word of thanks must go to the society for making it generally available.

R. CONRAD

Symposium on Human Factors in Equipment Design. The Ergonomics Research Society Proceedings, Volume II. Edited by W. F. Floyd and A. T. Welford. (Pp. 132 ; 17 figures. 21*s*.) London : H. K. Lewis. 1954.

The type of physiology which the medical student is usually taught does, in fact, bear some relationship to real life in so far as he learns something of the response of the human being to changes in the environment ; but in most of our medical schools he is still taught far too much of the minutiae of the anatomy of death, and psychology he is usually not taught at all.

In the last few years, notwithstanding its queer name, the Ergonomics Research Society has succeeded in bringing together anatomists, physiologists, and psychologists, in relating their three sciences to the practical problems of equipment design, and, in so doing, has given a fillip to a fused form of human biology. As a result of the last war, all three armed forces are very active in this field and have strong links with the Medical Research Council and the universities. In this, the Services are at least a generation ahead of most of private industry, whose idea of applied biology tends to be limited to first aid, the treatment of petty trauma, and pre-employment examinations.

The Ergonomics Research Society has now produced a second distinctively slim blue volume (the first was on fatigue), which is a collection of the best of the papers read at a symposium on the human factors in equipment design held in the University of Birmingham in 1951. It is a good selection of the papers read. There are 15 of them, and four are by visiting Scandinavian speakers at the symposium. The field covered includes the size and strength of the human body, its relationship (tinged either with pleasure or pain) to the chair on which it sits, the effect of climate, problems in the reading and understanding of indicator dials, and the general layout of equipment. Each paper is well documented with a reference list, and there are six good half-tone plates and many excellent diagrams.

This is an interesting and nicely turned out volume which is well worth a place on the industrial medical officer's shelf, and is much more readable than the medical tomes and official reports between which it may well be sandwiched. Moreover, it is well worth lending to the managing director himself to tell him, in an interesting way, what is going on in a field about which he may not yet have heard.

R. C. BROWNE

Mental Health and Human Relations in Industry. Edited by Thomas M. Ling ; Foreword by The Rt. Hon. Lord Horder. (Pp. xvi + 268 ; 11 figures. 21*s*.) London : H. K. Lewis. 1954.

The Social Psychology of Industry. By J. A. C. Brown. (Pp. 310. 2*s*. 6*d*.) London : Penguin Books Ltd.

Most of our time is spent either at home with our families, at work, or among the friends and acquaintances of our leisure. In each environment it is probably the people and our relationships with them which matter most to us and which, of all the aspects of our day-to-day existence, are most likely to affect our mental health. The psychiatrists have for the most part concentrated upon the family as a source of the satisfactions and provocations which affect the growing personality. Until recently the working and recreational groups have had scant attention from them as aetiological agents in mental illness, and have been considered, if at all, only in terms of therapy. Of these two groups the more critical and the more likely to cause trouble to the individual is the human environment at work.

Dr. Ling is a psychiatrist and medical director of the Roffey Park Institute of Occupational Health and of the Industrial Rehabilitation Centre. Dr. Brown is a psychiatrist with unique industrial experience. Their two books, therefore, should diagnose for us some of the human problems of industry and summarize what is known about the social and individual measures needed for their solution.

Roffey Park has changed and grown since its early post-war days and is now making a considerable contribution to the teaching of the social medicine of industry. A recent international course held there to consider mental health and human relations in industry suggested the need for " an account of current thought, teaching, and research, helpful in form and language to doctors, social workers, industrial managers, and entrants to industry from the universities ". In his book Dr. Ling and eight other authors attempt to meet this need and, considering the magnitude of their task, they do it very well.

In the 14 papers which make up the book most of the important features of the human environment at work are discussed. They range from the theoretical industrial sociology of group structure and group tensions, through an able but over-simplified treatment of aggressive behaviour in industry, to the more down-to-earth topics of selection procedures and the effects of the physical aspects of the work situation. Three papers are devoted to a consideration of the roles of those usually saddled with the human problems of industry : the personnel manager, the industrial medical officer, and the psychiatrist. The rapidly broadening responsibilities of management in the solution of these problems are emphasized in a final paper on " The Implications for Management ".

There is a brief note entitled " Society and Work " which is too short to do justice to the subject, and there are sections describing the teaching techniques which are in use and the rather slow progress of post-war research.

An important omission is an adequate discussion of economic factors in factory morale and in the worker-manager relationship. These factors and the related broad patterns of industry, of trade unionism, employer associations, and nationalization are very important, if only because they are the preoccupation of so many.

The bibliographies which follow each paper are well selected and form a most useful source of reference to the whole subject. The frequency with which the same not very significant works are referred to in successive papers serves only to illustrate the relative poverty of research in this field and the somewhat unsteady foundations of the subject. Fortunately this book is neither so complicated, so theoretical, nor so high powered as the imposing list of overseas editions and the introductory remarks led us to believe. We would have preferred a group of contributors chosen, perhaps, from a wider field than Roffey Park, but this parochialism is understandable and only slightly detracts from the usefulness of the work.

Dr. Ling has produced a book which will be of great value to all those working in industry.

While Dr. Ling aimed at the intellectuals and has produced a popular textbook, Dr. Brown has aimed at a much wider public and has produced a serious philosophical work. His book describes the decline in the social significance of work with the increasingly technical nature of industry. Through the ages this process has led to a situation where physical conditions in industry are often almost perfect but where " the need of the individual for status and function " remains unsatisfied and where the lunatic " rabble hypothesis " of every man for himself is generally accepted.

The author is concerned principally with the motivation and with the morale of the small groups of people whose relationships constitute the vital if informal organization of industry. He faces squarely the problem to which Sir George Schuster has recently drawn attention, that of the ease with which the increasingly powerful " social skills " of the industrial (or any other) psychologist may be perverted. He finds in industry good reasons for optimism and suggests that the help which is so often needed by sick industrial communities is not beyond the powers of ordinary people to give, nor is it the exclusive property of the consultant industrial sociologist.

Unfortunately the bibliography is so poor that many of the exciting references in this book cannot be followed. However, it is full of interesting material and will be very widely read.

The psychiatrist working in industry, like other doctors who work there, has got to prove to us that it is not uneconomic to base individual therapeutic services on anything but the family and the home. The material summarized in these books is not wholly successful in this plea. The physical hazards of the factory are plainly the responsibility of industry, but, for the industrial threats to mental health, responsibility is not so easily attributed. However, the need for social therapy in our industrial communities is the main concern of these books. In this they are wholly convincing.

E. MAURICE BACKETT

Textbook of Medicine. By various authors, edited by Sir John Conybeare and W. N. Mann. Eleventh edition. (Pp. xvi + 903 ; 40 figures, 31 *x*-ray plates. 37*s*. 6*d*.) London and Edinburgh : E. & S. Livingstone. 1954.

This well-known textbook has been extensively revised in order to bring it up to date, and extra articles upon the nephrotic syndrome, uraemia, the collagen diseases, and diseases of the intervertebral discs have been included. The text is strictly clinical in its character. It follows the classical pattern of description of diseases, those due to generalized infections, intoxications, or parasites coming first, followed by separate sections on diseases of the various systems of the body. Some of these sections have good, simple introductions on the anatomy and physiology of the relevant system, and on the ways in which they may be disturbed in disease. Occupational diseases are mentioned briefly under their appropriate systems. The descriptions are readable, concise, and quite sufficient for the student working for his qualifying examinations. In some cases they seem

unnecessarily long, and there is some lack of balance, thus enteric fever and diphtheria each get eight pages, while neoplasm of the lung and chronic bronchitis get respectively two and one and a half pages. The sampling process of a reviewer may not be quite random, but it revealed some unexpected errors and omissions. The article on pneumoconiosis is many years out of date and most misleading. The myths of circus movement in auricular flutter, and of the high protein content of nephritic oedema are perpetuated, and there is no mention of respiratory alkalosis or acidosis, nor of the Borst régime for anuria. The lucid account of the pathogenesis of hypertension makes no mention of the adrenals and salt retention, nor are insulin antagonists mentioned in diabetes. Details of clinical procedures such as lumbar puncture are deliberately omitted and perhaps one should not expect a reference to the cardiac catheter, but it is surprising to find no account of the technique of estimating venous pressure from the jugular veins. The index is full but has the curious property of redundant references to some subjects; there are seven references to sarcoidosis all on the same two pages and no reference to others such as shock or benign pericarditis.

Appendices on the treatment of disease by antibacterial drugs and by cortisone and A.C.T.H. summarize the position of these rapidly advancing fields at the time of going to press. Within the end covers there are tables of normal results of clinico-pathological tests (but expressed in the old milligrams per 100 millilitres instead of milli-equivalents), a conversion table from the apothecaries to the metric systems (in the text either or both are used), and a table of equivalents in official preparations of some popular proprietary drugs.

This all adds up to a useful book for students, but one which will not satisfy his scientific curiosity, or tell him where to go to do so. It will not tell him much about the principles of medicine, but it will guide his practice safely along orthodox channels.

C. M. FLETCHER

Review of Pneumoconiosis Abstracts, Vol. II. (Reprinted from the *Bulletin of Hygiene* for the years 1939 to 1950 inclusive); Foreword by Charles Wilcocks. (Pp. x + 518. 80*s*.) London: Sir Isaac Pitman. 1954.

The first volume of this work, which covered the years 1926 to 1938, contained 347 pages. The second volume, which brings the history up to 1950, contains 518 pages. Considering that the second period included the war years when very little was published, the rate of increase of literature on the subject of pneumoconiosis (as indeed on most subjects) is alarming.

All workers in the field who are striving to keep their heads above water in this spate of literature owe a debt of gratitude to the *Bulletin of Hygiene* and to Dr. E. L. Middleton who has again selected and arranged the abstracts. Another volume will undoubtedly be required in less than 12 years if it is not to be of unwieldy size, and it is to be hoped that it will be produced by the same capable hands.

B. M. WRIGHT

The Appraisal of Intelligence. By A. W. Heim. (Pp. 171. 12*s*. 6*d*.) London: Methuen & Co. 1954.

Dr. Alice Heim is well known as the author of two important intelligence tests, A.H.4 and A.H.5; the former was used in naval selection, the latter by the Civil Service Selection Board, and both have been the subject of a good deal of investigation. She is therefore clearly equipped to deal authoritatively with the testing of intelligence.

In this book she sets out to discuss the pitfalls of the would-be test constructor and user, and the result is an entertaining disquisition on her opinions of present-day psychologists and their theories. In particular, Dr. Heim makes a spirited attack upon the general usefulness of factor analysis and does not disguise her sympathy for the intuitive rather than the statistical approach to testing.

She starts with an inquiry into what is meant by intelligence, and suggests that as it is so flexible a concept it is misleading to consider it something which can be tested accurately. She prefers "intelligent activity" to intelligence, and believes that two qualitatively different forms of activity may be equally intelligent in a given situation. From this she goes on to castigate the factor analysts, the majority of whom she believes are prepared to label statistical artifacts "intelligence" without any valid grounds for so doing. After discussing the concepts of reliability and validity she moves to ground with which she is particularly familiar—the difference between results obtained from tests given with and without time limits. The book ends rather surprisingly with a chapter which says that "an intelligence test can be an exceedingly valuable instrument".

This useful little book should be read by all who make routine use of tests—and not only intelligence tests. It is probably too technical for those who have little testing experience, while to the research worker it will (or should) offer little that is novel. It leaves one with the impression that Dr. Heim is tilting at windmills. Here and there she admits that her objections may not be wholly general (as, for instance, when she admits that there are factor analysts whose claims are modest and whose conclusions are of value). It is certainly true that the term "intelligence test" is liable to introduce semantic difficulties because most people regard intelligence as synonymous with commonsense, whilst the majority of test constructors tend to narrow its meaning. It is also true that the "g" found in one battery of tests is often assumed to be more or less the same as the "g" found in another battery. It is true that the term "reliability" can be ambiguous and that there are several possible sources of unreliability when testing. Yet, in spite of these drawbacks, intelligence tests work; and if this point were made at the beginning of the book instead of at the end it would enable the reader to put Dr. Heim's criticisms more clearly in perspective.

To answer her objections in detail is beyond the scope of this note, but it may be useful to indicate the less pessimistic view. Most psychologists would agree that the label "intelligence test" is unsatisfactory and that "g test" is not much better. Most serious workers are

not much concerned with the label : their interest is in the usefulness of the test for some particular purpose, whether it be in assessing the educability of an apparent defective or in selecting an officer or executive. Argument about terminology is essentially sterile ; to use a test, on the other hand, is dynamic. The danger of generalizing about the nature of psychological factors found in any particular analysis is certainly very real, but if certain tests constantly show approximately the same content in different situations it is obviously convenient to consider them as measuring with some degree of accuracy a factor (or classification category) of which use can be made without worrying whether it is a statistical fiction or an actual entity. For example, there is a striking ubiquity about the figures found on factor analysis of test batteries which include progressive matrices (1938) : studies in the Services and in industry have given this test loadings of about 0·6 to 0·7 on the general factors of many different batteries analysed by different methods. This suggests some similarity of character between the general factors, and further statistical investigation reinforces the impression that the test is, in fact, measuring a " sense " which is common to many intellectual situations—not, indeed, the commonsense of everyday life, but certainly a common ability which is no more and no less real.

Dr. Heim dwells on the possible sources of unreliability. More surprising is the extent to which tests are reliable when subjects are exposed to conditions which are normally considered disturbing. For instance, menstruation as a cause of test variation was thoroughly investigated in the Army ; on eight standard tests no significant difference in score was induced, and at one other practical mechanical test there was, in fact, a rise in score during menstruation. Unreliability obviously cannot be ignored, and it must continue to be the subject of research ; equally, it should not be over-emphasized.

There are few who will disagree with a plea for better tests, more careful testing, better validation against objective criteria, and caution in assumptions about the nature of the abilities displayed by test performance. It would be a pity if over-emphasis on caution should lead to stultification or reluctance to use tests because of the fear of a mistake. A. G. P. ELLIOTT

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Hospital and Community. By Thomas Ferguson and A. N. MacPhail. (Pp. 157. 9*s*. 6*d*.) London : Oxford University Press. 1954.

Microbiology : An Introduction. By Ernest A. Gray. (Pp. 175 ; 24 illustrations. 10*s*. 6*d*.) London : Crosby Lockwood. 1954.

Intoxications et Maladies Professionelles. By Léon Dérobert. (Pp. 1,556 ; 76 illustrations. Fr.frs. 8,800.–.) Paris : Éditions Médicales Flammarion. 1954.

A Synopsis of Forensic Medicine and Toxicology, 3rd ed. By E. W. Caryl Thomas. (Pp. viii + 180. 12*s*. 6*d*.) Bristol : John Wright. 1954.

A Practical Manual of Diseases of the Chest, 4th ed. By Maurice Davidson. (Pp. x + 647 ; 255 illustrations. 84*s*.) London : Oxford University Press. 1954.

First Report of the Joint Committee on Human Relations in Industry, March 1953 to March 1954. Department of Scientific and Industrial Research and Medical Research Council. (Pp. 16. 1*s*.) London : H.M. Stationery Office. 1954.

Annual Report 1953 of Tata Industries Limited. Department of Industrial Health. (Pp. 17.) 1954.

Expert Committee on Environmental Sanitation. Third Report. (W.H.O. Technical Report Series, 1954.) (Pp. 25. 1*s*. 9*d*.) London : H.M. Stationery Office ; Geneva : World Health Organization. 1954.

There is Life in the Old Dog Yet. By John P. Rainsbury. (Pp. 45 ; 19 illustrations. 5*s*.) Darlaston : Rubery Owen. 1954.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the abstracting Journal,* Abstracts of World Medicine, *published by the British Medical Association. The abstracts are divided into the following sections : toxicology ; industrial physiology ; industrial lung disease ; industrial skin diseases ; accidents and orthopaedic surgery ; industrial ophthalmology ; environment ; general. Not all sections will necessarily be represented in any one issue)*

INDUSTRIAL TOXICOLOGY

Acute Inhalation Toxicity of Beryllium. IV. Beryllium Fluoride at Exposure Concentrations of One and Ten Milligrams per Cubic Meter. STOKINGER, H. E., SPIEGL, C. J., ROOT, R. E., HALL, R. H., STEADMAN, L. T., STROUD, C. A., SCOTT, J. K., SMITH, F. A., and GARDNER, D. E. (1953). *Arch. industr. Hyg.*, **8,** 493.

In continuation of their previous work on the toxicity of beryllium (*Arch. industr. Hyg. occup. Med.*, 1950, **1,** 379 and **2,** 25 ; *Abstracts of World Medicine*, 1951, **9,** 132 and 22), the authors now describe the acute effects of the inhalation of an aerosolized aqueous solution of beryllium fluoride on dogs, cats, albino rats, albino mice, guinea-pigs, and rabbits. The experimental conditions were similar to those described in the previous papers, the concentration of beryllium fluoride was 10 mg. per c. metre in a first experiment and 1 mg. per c. metre in a second, and the period of exposure was 15 and 207 days respectively.

The effects included pulmonary changes similar to those produced by beryllium sulphate, and a macrocytic anaemia not prevented or cured by administration of vitamin B (cyanocobalamin), "lextron" (a liver–stomach concentrate with a ferrous salt), or folic acid. There was also a decrease in the number of mature polymorphonuclear leucocytes and an increase in that of immature forms. A considerable amount of beryllium accumulated in the bones in a concentration exceeded only in the lungs and the pulmonary lymph nodes. Beryllium fluoride was found to be much more toxic than beryllium sulphate. *John Pemberton*

Serious Poisoning by Hexachlorocyclohexane. Clinical and Laboratory Observations on Five Cases. DANOPOULOS, E., MELISSINOS, K., and KATSAS, G. (1953). *Arch. industr. Hyg.*, **8,** 582.

There have been few reports of acute poisoning with benzene hexachloride. In the summer of 1951, 79 persons of various ages and both sexes living in the area of Carpenissi, Greece, suffered from poisoning due to the improper use of an insecticide composed of benzene hexachloride (40%) and magnesium silicate (60%), which they had sprinkled on their bedding and on the walls of their houses.

In this paper the authors describe the clinical and laboratory findings in 5 of the cases, one of which was fatal, examined in detail at the University Medical Clinic, Athens. The chief symptoms were lassitude, headache, and myalgia, followed by intestinal colic, diarrhoea, and stomatitis. Later, neurological signs appeared, including delirium, choreic and athetoid movements, tremor and convulsions, signs of upper motor neurone damage, and cerebellar signs. Optic neuritis occurred in 3 cases and one boy became blind from complete atrophy of the optic nerve. There were also electrocardiographic changes, toxic inhibition of erythrocyte maturation, an increase in blood chloride levels, a raised erythrocyte sedimentation rate, and, in the fatal case, laboratory and post-mortem evidence of liver damage. The patients were treated with "adrenal preparations", blood transfusion, vitamins B and C, and a high protein diet. Of the 79 persons affected, 18 were seriously ill and 6 died. Convalescence in most cases was very slow.
John Pemberton

Toxicity Studies of Acetone Cyanohydrin and Ethylene Cyanohydrin. SUNDERMAN, F. W., and KINCAID, J. F. (1953). *Arch. industr. Hyg.*, **8,** 371.

Ethylene cyanohydrin is a stable material, the cyanide and hydroxyl groups being attached to different carbon atoms ; it is relatively non-toxic, and there is no record of industrial intoxication. Acetone cyanohydrin on the other hand, in which the cyanide and hydroxyl groups are attached to the same carbon atom, is readily dissociated into its components, acetone and hydrogen cyanide, and it is consequently a highly toxic material. The results of animal experiments, here reported from Jefferson Medical College, Philadelphia, support the hypothesis that this toxicity is due to the release of hydrogen cyanide *in vivo*. The nitrite-sodium thiosulphate therapy in common use for hydrogen cyanide poisoning has proved effective in the treatment of rats poisoned with acetone cyanohydrin.

Two cases in which death was probably due to industrial intoxication by acetone cyanohydrin are described. *M. A. Dobbin Crawford*

Cadmium Intoxication. Clinical Report of an Acute Accidental Group Exposure. AMDUR, M. L., and CAPUTI, R. A. (1953). *Industr. Med. Surg.*, **22**, 561.

The authors describe 4 cases of cadmium poisoning caused by an industrial process in which metallic cadmium wire was melted and blown against a rotating spindle in order to coat the latter with the metal. Only about 40% of the metal was deposited and as there was no exhaust ventilation significant amounts of cadmium contaminated the atmosphere. The 4 workers who developed symptoms of cadmium poisoning were the process operator, a maintenance welder and his assistant who worked about 10 feet (3 m.) away from the spindle, and a female clerical worker on the floor above whose desk and chair were near a ventilating duct which communicated with the workroom below in the immediate vicinity of the welding. The process began at 11.0 a.m. and was completed by 2.30 p.m., during which time about 10 lb. (4·5 kg.) of cadmium wire were used. It is believed that the operator was exposed to metallic cadmium while the other three were exposed to cadmium-oxide fume generated from the airborne cadmium as it entered the welding arc. All the patients complained of cough and pain or a sense of constriction in the chest, beginning either during, or a few hours after, exposure ; other symptoms were malaise, nausea, vomiting, and headache. The welder, who was most severely affected, had marked breathlessness, and this was also a feature in the operator, whose symptoms, however, were less severe.

Inflammation of the fauces and nasopharynx was noted in all 4 patients and in 3 the conjunctivae were congested as well. In chest radiographs taken after exposure there was an increase in the vascular markings in all 4 cases, compared with similar radiographs taken before exposure. The electrocardiogram showed sinus bradycardia in 3 cases and in the case of the welder a P–R interval up to 0·24 second. Vital capacity, which was reduced in each case, returned to normal during the recovery period, which varied from one week to 6 weeks.

Urinary excretion of cadmium continued for periods varying from 3 to 7 weeks, depending on the severity of the symptoms.

Although the respiratory system was affected many of the symptoms were not primarily respiratory. It is suggested that cadmium inactivates cholinesterase by combining with the sulphhydryl portion of the molecule ; this would account for the bradycardia, heart block, abdominal pain, nausea, vomiting, and sense of constriction in the chest which were noted in all the cases.

After this incident exhaust ventilation was fitted to the plant and an airline helmet was provided for the operator. In spite of these precautions air samples taken in the breathing zone of the operator, but outside his helmet, revealed a concentration of cadmium in air which was about 11 times the maximum allowable (0·1 mg. per cubic metre of air) ; 10 feet away from the operator the concentration was a little above the maximum allowable.

W. K. S. Moore

INDUSTRIAL LUNG DISEASE

Bronchial Carcinoma in Dusty Occupations. Observations in Boiler Scalers and Grain Dockers. DUNNER, L., and HICKS, M. S. (1953). *Brit. J. Tuberc.*, **47**, 145.

It would appear, if statistics are to be believed, that the incidence of bronchial carcinoma is higher in patients suffering from asbestosis, siderosis, and the effects of chrome inhalation than in controls, whereas the incidence in patients suffering from silicosis is no higher. Pneumoconiosis occurs in dockers handling grain and in boiler scalers, and the present authors, from the Chest Clinic, Hull, describe 26 cases of bronchial carcinoma occurring in men working in these trades. Of the 26 patients (20 of whom were grain dockers), 14 were seen in 1951–52, a period when the number of deaths from bronchial carcinoma among the general population of Hull was on the increase. There are 5,000 dockers in Hull and only half of these are exposed to dusts ; among the other half, and this is probably significant, not one case of bronchial carcinoma was seen. The authors believe that exposure to dust is an aetiological factor, but they admit that the unknown factor responsible for the increased incidence in the general population also played some part. In 5 of their patients there was histological evidence of pneumoconiosis but only in one (a boiler scaler with obvious silicosis) was there radiological evidence of this condition. There were no non-smokers or heavy smokers among their patients.

Paul B. Woolley

Farmer's Lung. STUDDERT, T. C. (1953). *Brit. med. J.*, **1**, 1305.

Writing from the Cumberland Infirmary, Carlisle, the author discusses the natural history of the condition conveniently termed "farmer's lung", and briefly reviews the literature. The symptoms of this disorder are breathlessness, cough, cyanosis, and slight pyrexia, accompanied by the presence of widespread crepitations in the lungs, and they make their appearance soon after exposure to the dust of mouldy hay. The *x*-ray appearances show increased lung markings, with additional soft shadowing. Spontaneous recovery is usual in about 2 months, but there may be residual emphysema in some cases. It is reputed among farmers occasionally to have caused sudden death, and also to be the cause of broken-windedness in horses. An enquiry showed that most rural doctors are familiar with the disease, especially in north-west England where it is common, but as it usually resolves spontaneously cases are not often seen in hospital.

In the discussion of aetiology and differential diagnosis, distinction is made between farmer's lung and asthma caused by mouldy hay dust ; the former condition usually develops within 24 hours of exposure, and presents as a mild acute pulmonary oedema without cardiac distress. Rigor and vomiting are common at the onset. Recovery from the condition, both clinically and radiologically, is gradual, and may take up to 3 months. In some of the author's cases moulds were isolated from the sputum and often corresponded with those found in the hay

dust, but they were not thought to be specifically causal; nor were specific skin-sensitivity reactions to them obtained, as was the case in a patient whose symptoms were those of asthma following exposure to mouldy hay. Consolidation signs, pleurisy, and haemoptyses do not occur, and serve to distinguish pneumonia from farmer's lung. Aspergillosis is distinguished by the occurrence of dense infiltration and cavitation, and by the presence of actively growing mould in the sputum.

The condition is considered to be a non-specific reaction of the lung to a variety of irritants, and the similarity of the disease to certain other occupational diseases (for example, coniosporiosis, weaver's cough, byssinosis, and diffuse granulomatous pneumonitis) is stressed. A series of 6 personal cases is described.

L. W. Hale

The Morphology and Pathogenesis of Pumice Pneumoconiosis. FERRARA, A., and FARAONE, G. (1953). *Riv. Infort. Mal. prof.*, **40**, 453.

This is a general account of the pathology and histology of pneumoconiosis due to pumice dust, based on the post-mortem findings in 4 cases, which are not individually described. The middle zones of both lungs were mainly affected, the apices escaping as a rule. Two types of macroscopic appearance were found—a linear fibrosis, corresponding to the radiological "reticulation", and a massive fibrosis. Unlike other forms of silicosis, the stage of nodulation seems to be entirely absent; the author considers that this may be associated with the low content of free silica (1·85%) in pumice dust. This may also account for the long latent period, perhaps 20 to 30 years, before symptoms develop. Tuberculosis was not found in association with pumice-dust silicosis. Pleural fibrosis was usually present, and also marked enlargement of the mediastinal lymph nodes, but there was no evidence of bronchiectasis, although there was generalized emphysema.

Histologically, the condition did not seem to differ greatly from other forms of silicosis; widespread connective-tissue thickening interspersed with mineral deposits and without extensive cellular infiltration was characteristic. There was no focal emphysema. The bronchial mucosa was greatly swollen and infiltrated with masses of cells and phagocytes containing mineral particles; a true obliterating granulomatous bronchitis was present. Local circulatory obstruction appears to lead eventually to extensive small arterio-venous shunts, and this phenomenon may explain the pulmonary venous congestion and deficient oxygenation characteristic of silicosis. Pumice dust, containing little free silica, does not quickly set up a local irritant process, but is drained into the lymph nodes and blood stream, with involvement of other organs, including the pleura, and alteration in the blood plasma (dysproteinaemia). Massive fibrosis is not considered to follow bronchial obstruction, but to be due to the arterio-venous lesions already mentioned.

L. G. Norman

A Note on Extrapulmonary Histology in Pumice Worker's Disease. FERRARA, A., and FARAONE, G. (1953). *Riv. Infort. Mal. prof.*, **40**, 468.

Silicosis due to pumice dust affects organs other than the lung, the multi-visceral involvement which occurs justifying, in the authors' opinion, the designation "silicotic disease". Histological changes found post mortem in the liver, spleen, and kidneys in 4 cases are described. The liver showed a diffuse reticulo-endothelial hyperplasia; there were widespread and abundant deposits, of a microcrystalline mineral, mainly concentrated in the histiocytes of the portal spaces and the Kupffer cells. The authors consider that the dust is carried to the liver and deposited in crystalline form throughout the process. In one case there was also a diffuse amyloidosis. There was moderate enlargement of the spleen, with hyperplasia of the reticular elements of the pulp, reduction in the number of follicles, and a moderate degree of congestion. Deposits of microcrystalline siliceous material were present, while numerous small infarcts were observed in one of the 4 cases. There was no siderosis. The kidneys showed a widespread deposit of microcrystalline material, less marked than in the liver and spleen, lying mainly in the capillaries of the glomeruli and cortical connective tissue. There was also an early generalized fibrosis, particularly of the glomerular vascular network, with congestion and cellular deposits in and around the tubules. The latter changes were probably associated with alteration in the blood protein levels, mainly due to abnormal excretion of serum albumin.

L. G. Norman

Conference on Silicosis

A conference on silicosis and occupational chest diseases, jointly sponsored by the McIntyre Research Foundation, of Toronto, Canada, and the Saranac Laboratory, of Saranac Lake, New York, has been arranged for Monday, Tuesday, and Wednesday, February 7, 8, and 9, 1955, in the Town Hall at Saranac Lake.

The papers to be presented in the five full sessions will all report on original work conducted or sponsored by either the McIntyre Research Foundation or the Saranac Laboratory. In addition there will be papers presented by guest lecturers.

Doctors, scientists, and business men concerned with the problems of occupational chest diseases in all parts of the United States, Canada, and foreign countries are invited to attend.

The business arrangements including reservations will be handled by Norman R. Sturgis, Jr., and the treasurer will be Clarence L. Wagner, both of the Trudeau-Saranac Institute staff. All communications concerning the conference should be addressed to Mr. Sturgis, Saranac Laboratory, Saranac Lake, New York.